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PSYCHOLOGICAL DISTRESS FOLLOWING OESOPHAGEAL CANCER TREATMENT: IS THERE A NEED FOR PSYCHOLOGICAL SUPPORT?

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PSYCHOLOGICAL DISTRESS FOLLOWING OESOPHAGEAL CANCER TREATMENT: IS THERE A NEED FOR PSYCHOLOGICAL SUPPORT?

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Oesophageal cancer is associated with a poor prognosis, an extensive treatment pathway and a difficult recovery process. Previous studies have shown that oesophageal cancer patients suffer from great physical impact of the disease and treatment from the early rehabilitation process up to ten years following curatively intended treatment. Thus, affecting all aspects of their life situation. In addition, major adjustments in food intake and eating habits are required, negatively affecting the patients' wellbeing. Even though evidence regarding poor recovery and deterioration in Health related quality of life, have been established during the past years. The psychological distress experienced by oesophageal cancer patients has not yet been thoroughly investigated. Therefore, the overarching aim of this thesis was to describe the psychological distress experienced by patients undergoing curatively intended treatment for oesophageal cancer in an attempt to evaluate if psychological support is needed?

Study I was a cross-sectional study using data from a prospective cohort study carried out at St Thomas' Hospital in London, England. Using data from the data collection at St Thomas' Hospital, **Study II** was longitudinal in design. **Study III** used data from a prospective cohort study based on Swedish data. **Study IV** was a qualitative interview study carried out in Sweden. **Studies I-III** used self-report questionnaires aiming to assess anxiety and depression (using the The Hospital Anxiety and Depression scale) and aspects of emotional functioning (i.e., four items; tension, worry, irritation and depressed mood) from the EORTC QLQ-C30. In **Study I** anxiety and depression were assessed pre-surgery, in **Study II** the same outcomes were measures at pre-surgery and then at six and 12 months post-surgery. In **Study III** aspects of emotional functioning were assessed at six months and five years following the operation. In **Study IV** in-depth interviews were completed at six months post-surgery. Logistic regression models were carried out in studies **Study I** and **III**, in order to assess the association between potential clinical and socio-demographic risk factors and anxiety and depression (**Study I**) or aspects of emotional functioning (**Study III**). In **Study II** mixed-effects models were used to evaluate the influence of clinical and socio-demographic variables on psychological distress (i.e., anxiety and depression). The interviews in **Study IV** were analysed using qualitative content analysis.

A significant proportion of patients report anxiety and depression prior to surgery and then at six and 12 months following treatment (**Studies I** and **II**). Anxiety symptoms seem to remain stable from prior to surgery and up to 12 months post-surgery. However, depression symptoms seem to increase from pre-treatment to six months following surgery and then

level off at 12 months after treatment (**Study II**). Younger age, female sex, limitations in activity status and dysphagia are some of the risk factors observed for psychological distress at the different time points (**Studies I and II**). Further, tension, worry, irritation and depressed mood are prevalent symptoms at six months and even after five years post-surgery **Study III**). Risk factors included for example low educational level. The patients' narratives at 6 months following oesophageal cancer surgery described reflections of undergoing a crisis reaction (final theme, **Study IV**).

In conclusion, oesophageal cancer patients report psychological distress during the treatment trajectory, partially influenced by factors related to previous known risk factors for psychological morbidity. Considering the findings of this thesis, the many patients suffering psychological distress throughout recovery and beyond, are likely in need of targeted psychological support to improve their overall well-being and adaptation to the consequences of this disease and treatment.

LIST OF SCIENTIFIC PAPERS

- I. Hellstadius Y, Lagergren J, Zylstra J, Gossage J, Davie A, Hultman CM, Lagergren P, Wikman A.
Prevalence and predictors of anxiety and depression among esophageal cancer patients prior to surgery.
Diseases of the Esophagus 2016; 29(8):1128-1134.
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A longitudinal assessment of psychological distress after oesophageal cancer surgery.
Acta Oncologica 2017; 56(5):746-752.
- III. Hellstadius Y, Lagergren P, Lagergren J, Johar A, Hultman CM, Wikman A.
Aspects of emotional functioning following oesophageal cancer surgery in a population-based cohort study.
PsychoOncology 2015; 24(1):47-53.
- IV. Hellstadius Y, Lindqvist O, Malmström M, Lagergren P, Sundbom M, Wikman A.
Reflecting a crisis reaction: narratives from patients with oesophageal cancer about the first six months after diagnosis and surgery.
Manuscript.

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LIST OF ABBREVIATIONS

CRT	Chemoradiotherapy
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire –Core 30
HADS	Hospital Anxiety and Depression Scale
MDM	Multidisciplinary meeting
MDT	Multidisciplinary team
OR	Odds ratio
SD	Standard deviation
SECC	Swedish Esophageal and Cardia Cancer database
STH	St Thomas' Hospital
PCA	Principal component analysis
PROM	Patient Reported Outcomes Measures

FOREWORD

With a clinical background in palliative care, I am deeply committed to improving the care of individuals struck by cancer. It is my conviction that no person should suffer or die from an illness without being autonomously involved in every step along the illness trajectory. I believe this is not only a prerequisite for qualified cancer care, but also a basic human right. In order to accomplish this, I strongly believe that the psychological consequences a person might suffer following a cancer diagnosis, through treatment and rehabilitation, should be routinely assessed. To be able to intervene when necessary it is important to identify those persons who are at greatest risk of psychological morbidity, before the consequences of suffering from distress have negatively affected the person's ability to recover.

One fundamental part of change is motivation. During my work on this thesis I have had the great privilege to meet and interact with many patients who have generously shared their experiences of this disease and treatment. When I have asked the patients included in this thesis what made them so determined to get through the extremely challenging treatment, they all answered that the driving force was the motivation to survive the cancer. But I ask myself, what happens then? What happens after the advanced treatments, when the patients have to start to cope with their new life situation? What happens when health care professionals consider a person a "cured case"? Following the work I have carried out during my doctoral studies, I am convinced that "then" is the time we really have to focus on, to be motivated to change, in order to improve the cancer care for these patients.

The most striking explanation I ever heard was from an oesophageal cancer survivor who described his new life as:

"There is no way back, only a way forward"

Ylva Hellstadius

Stockholm April 24th 2017



"A long way"

1 INTRODUCTION

Oesophageal cancer is the 6th most common cause of cancer death globally. It is considered a rare disease in Sweden but more common in the United Kingdom. Approximately 600 cases are diagnosed in Sweden yearly [1], while 8,900 cases are diagnosed yearly in the United Kingdom (UK) [2] and 480,000 new cases worldwide [3]. Oesophageal cancer is aggressive and due to the asymptomatic onset, many patients are diagnosed in the late stages of the disease. Subsequently, only about 25% of the yearly cases are eligible for curatively intended treatment and 75% receive palliative treatment [4, 5]. This thesis focuses on the patients who have undergone curatively intended treatment for oesophageal cancer.

There are four main reasons why oesophageal cancer represents a particularly distressing cancer disease; 1) the poor prognosis, 2) the severe treatment pathway for curable tumours, 3) the challenging post-operative recovery and, 4) the life changing experiences related to alterations in eating habits. While mortality, morbidity and health-related quality of life (HRQOL) in oesophageal cancer patients have been thoroughly investigated during the last decade [6-8], far less is known about the psychological consequences of the disease and treatment [9]. There are some previous publications that have indicated increased psychological distress in this cancer group [10-13]. However, the course and burden of psychological distress experienced by oesophageal cancer patients, the risk factors associated with poor psychological recovery and the timing of potential psychological support have not yet been clarified in the literature.

This thesis is based on four original studies, focusing on psychological distress, defined as anxiety, depression and aspects of emotional functioning, assessed by self-report in oesophageal cancer patients from diagnosis up to five years following curatively intended treatment. The thesis results also include the patients' own narratives about their adaptation from the time of diagnosis until six months post-surgery, in an attempt to complement the findings from the cohort studies by including the patients' own voices in describing their experiences and adaptation during the illness trajectory. Whether this patient group is in need of psychological interventions in order to improve their post-operative adjustment, as part of improving the course of care and long-term outcomes, is also discussed.

All data included in this thesis were collected in Sweden or in England. Therefore, it is very important to consider, when reading this thesis, that the course of treatment including investigations, surgical and medical procedures, as well as follow-up information, mirror the

management of oesophageal cancer in Western society in general and in Sweden and England in particular. Thus, the thesis findings should be interpreted in the light of this context.

2 BACKGROUND

2.1 OESOPHAGEAL CANCER

2.1.1 The “food pipe”

The oesophagus is the tube that transfers food from the mouth to the stomach. The tube consists of several muscular layers and is approximately 18-26 cm long, from the upper to the lower sphincter. The sphincters main function is to prevent gastro-oesophageal reflux or food from coming up from the stomach into the mouth. The oesophagus is surrounded by many vital organs within the thorax, such as the trachea (the windpipe), the main stem bronchus, the lungs, the aortic arch and the heart. The close proximity to these vital organs makes surgery in this area complicated and increases the risk of severe complications such as bleeding or dangerous and rapid infections [14].



“Anatomic illustration of the oesophagus and the bowel”

2.1.2 Risk factors

There are two main histological types of oesophageal cancer, adenocarcinoma and squamous cell carcinoma, with quite different pathological pathways, risk profiles and incidence trends [15]. Adenocarcinoma is usually found in the lower part of the oesophagus or the gastro-oesophageal junction [16] and the most established risk factors are gastro-oesophageal reflux, obesity [17] and Barrett's oesophagus (i.e., abnormal conversion in the mucous membrane of the oesophagus) [18]. The incidence of adenocarcinoma is increasing worldwide and to date the United Kingdom has the highest overall incidence of adenocarcinoma in the world [2]. Squamous cell carcinoma is usually located in the upper or middle part of the oesophagus and known risk factors are tobacco smoking, high alcohol intake and poor socio-economic status [19, 20]. During recent years a stable or decreasing incidence of squamous cell carcinoma has been observed in the Western world even though this histological type is still the dominant type worldwide. However, adenocarcinoma has now surpassed squamous cell carcinoma in the Western world, probably due to lifestyle factors such as dietary intake, tobacco smoking, alcohol consumption and obesity [7]. This is important to consider due to the distribution of histological type in the samples included in this thesis (percentages of patients diagnosed with adenocarcinoma in Study I 90%, Study II 94%, Study III 76% and Study IV 100%), which mirrors the incidence trend in the Western world. It is also important to mention the sex difference in incidence when interpreting the results of this thesis. Both adenocarcinoma and squamous cell carcinoma are more common in men than women. However a 3:1 male predominance ratio is observed for squamous cell carcinoma, while a 7:1 predominance ratio is seen for men in adenocarcinoma [21-23]. The high prevalence of males compared to females is also reflected in the studies included in this thesis; 81%, 76%, 82%, 80%, for Studies I-IV, respectively.

2.1.3 Early symptoms

Oesophageal cancer is a "quiet disease" meaning that the majority of patients experience the first symptoms when the tumour has grown for a rather long time, due to the elastic capacity of the oesophagus. Therefore, the majority of patients are diagnosed in the late stages of the course of the disease, sometimes when the disease has already started to metastasise. For those patients who experience symptoms the most common symptom is swallowing difficulties followed by weight loss, heartburn and pain or a sense of discomfort when swallowing food [24]. However, the first symptoms have been described as very vague; 'I wasn't sick. I only had a thickness in my throat' in interview studies with survivors of oesophageal cancer [25]. Due to the silent onset of the disease, many patients have described

the shock of being diagnosed with such a severe cancer without any physical warnings; ‘I knew nothing about my condition before I got the diagnosis. I was completely dumbfounded’ [25].

2.1.4 Diagnosis

When a tumour in the oesophagus is suspected, the patient is referred to a special oesophago-gastric clinic where an extensive investigation starts [26]. The course of investigation typically includes gastroscopy with biopsies, a computed tomography, a PET-scan and endoscopic ultrasound in order to evaluate the tumour. In addition, the patient also undergoes a range of physical functioning tests to evaluate their performance status. Following this extensive assessment the multidisciplinary team ([MDT] including oncologists, pathologists, radiologists, surgeons, dieticians and nurses), together with the patient, decides the treatment pathway, according to the patients pre-assessment status [26].

Approximately 480,000 patients are diagnosed with oesophageal cancer yearly, worldwide [3]. Of these, 8,900 are diagnosed in the UK [2] and 600 in Sweden (oesophageal and gastro-oesophageal junction cancer combined) [1]. Due to the low number of cases, oesophageal cancer is considered a rare cancer disease, yet an aggressive cancer with a poor prognosis [3]. In interview studies, the shock of being diagnosed with oesophageal cancer has been described as a death threat associated with strong emotions, due to the confrontation with the fatal nature of the disease and information about the aggressive treatment regime [27]. McCorry et al [28] have described this shock as ‘coping with a death sentence’.

At diagnosis only approximately 25 % of the patients are undergo curative treatment, usually, surgery in combination with chemo- and/or radiotherapy, although very early tumours are treated with endoscopic removal or surgery alone. Further, 75 % of the patients have too advanced disease or are not considered fit enough to survive the demanding curative treatment pathway [24]. Despite curative treatment only 30-50% of the patients survive more than five years [4, 5] and approximately 18% survive more than 10-years post-surgery [29]. The risk of tumour recurrence is highest during the first year after treatment [30-32]. Consequently, the thorough pre-treatment assessment in combination with the uncertainty makes the initial phase of the illness trajectory, following the diagnosis, a vulnerable time for the patients and their relatives. This waiting time, between diagnosis and operation has been described by the patients as “being in limbo” with feelings of paralysing fear and loneliness [33]. However, in a recent large-scale cohort study, the mental health consequences of the

waiting time for cancer treatment among oesophageal and gastric patients were shown to be highly dependent on the patients' prior history of psychiatric vulnerability. Patients with a pre-existing mental disorder and increased waiting time for treatment (>18 days), were more likely to consume psychiatric hospital care (i.e., hospital visits and medication prescriptions) during the first year of illness than were patients without a pre-existing mental disorder. In addition, patients without a pre-existing mental disorder exposed to a longer waiting time (18-29 days), had a lower risk of new onset mental disorder during the first year, as compared to patients with a shorter waiting time (9-17 days). The explanation for the surprising inverse association remains unexplained. However, hypothetical explanations that longer waiting time might facilitate psychological adaption, among patients without pre-existing mental disorder, or that a quick management might affect the quality of the treatment have been presented [34].

2.1.5 Treatment

Following a diagnosis of oesophageal cancer in Sweden or the UK, the patient's diagnostic assessments are discussed by the MDT in order to provide the best available treatment for each individual patient. The MDT discusses each patient thoroughly in a recurrent conference (i.e. multidisciplinary meeting [MDM]) with the overarching aim of providing the best available care plan for the patient based on the patient's tumour stage (TNM-stage) and tumour location, performance status, co-morbid diseases, and most importantly, the patient's own preferences [2, 26]. Treatment with curative intent is only indicated when the cancer has not spread and the patient is considered physically fit to be able to undergo the extremely challenging procedure of an oesophagectomy (i.e., resection of the oesophagus).

Unfortunately, 75% of patients are diagnosed with a too advanced tumour stage or are too burdened by co-morbid diseases, to be able to undergo such an advanced treatment regime. This means that the majority of patients are offered palliative treatment following the diagnosis, in an attempt to control symptoms and sometimes prolong life [24, 26].

2.1.5.1 Curatively intended treatment

The curatively intended treatment strategy includes radical surgery, where the whole or parts of the oesophagus are removed (i.e., resected) and replaced by a gastric substitute, usually the stomach [26, 35]. Oesophagectomy is one of the most extensive standard surgical procedures in Sweden and in the UK, and the only chance of cure for many patients suffering from a tumour in this area [26, 36]. The main reason why the surgery is considered such an advanced procedure is the inaccessibility of the oesophagus, as it is close to other vital organs and the surrounding structures, and sensitive to infections. Therefore, the risk of post-operative

complications is high and mortality rates following the operation have been reported to be in the region of 3-14% [37]. In addition, chemotherapy or chemoradiotherapy prior to the operation (i.e., neoadjuvant therapy) is today given to the majority of patients as a part of the curatively intended treatment regime in Sweden and in the UK [38]. Neoadjuvant therapy complements the localised surgery with a systemic effect, which potentially eliminates micro metastasis from spreading and shrinks the tumour. This has benefits both for the short-term, by reducing preoperative symptoms caused by the tumour (e.g., dysphagia) and longer-term effects, for example reducing the risk of disease relapse [26]. In Sweden adjuvant chemotherapy e.g., chemotherapy after the operation has no role in the curative treatment regime [26]. However, in the UK, the majority of patients undergo chemotherapy both before and after the surgery (i.e., perioperative chemotherapy), especially those patients who are diagnosed with a tumour in the lower part of the oesophagus, or in the gastro-oesophageal junction (i.e., where the stomach meets the oesophagus). The main reason for perioperative chemotherapy is to lower the risk of cancer recurrence [39]. Moreover, radiotherapy can also be administered before or after the operation and often in combination with chemotherapy (e.g., chemoradiotherapy). The reason for this is to obtain local tumour control, but the procedure is associated with side-effects, for example impaired wound healing or complications during the operation [26]. Despite treatment with curative intent, only approximately 30-55% of patients are alive after five years [5, 40].

Several treatment side-effects have been reported after surgery and chemotherapy, for example nausea, vomiting, diarrhoea, and dumping, [27, 33]. Furthermore, the extreme tiredness associated with chemotherapy (i.e., fatigue), has been described as long-lasting in interview studies with oesophageal cancer patients, forcing the patients to adapt their whole life to this challenging symptom [25]. Larsson et al [41] explored the side-effects of undergoing radiotherapy among patients with head and neck cancer. The patients described the feeling of a burning throat and a sour or dry mouth that made it painful to eat and swallow. Subsequently, the treatment largely affects patients' physical body, psychological status and social situation [28]. Carey et al [42] described the mobilisation of different coping strategies (both adaptive and maladaptive) in oesophageal cancer patients in order to manage the new and difficult life situation. Suggestions that the post-treatment experience should be likened with a chronic illness, rather than a temporary situation, would possibly allow mourning of past bodily perceptions and capabilities earlier, thus facilitating adaptation.

2.1.6 Post-operative course

Following the surgical procedure patients stay in the intensive care unit initially and are later moved to a surgical ward. The initial post-operative care focuses on pain management, physical mobilisation and re-starting oral intake [26]. The risk of in-hospital complications is approximately 29-50% [43, 44]. Medical complications e.g., pneumonia, respiratory insufficiency or sepsis are more common than to surgical complications e.g., bleeding, or leakage in the area where the substitute has been connected with the remaining part of the oesophagus (i.e., the anastomosis) [45].

The majority of patients suffer from major postoperative weight loss [46] and all are in need of both dietary information support from dieticians and additional nutrition for an extended time after the operation [26]. After discharge from the hospital the patient's post-operative care continues at home and is regularly followed up by a contact nurse ('kontaktsjuksköterska' in Swedish) and a dietician. In the case of severe complications, patients in need may be admitted to the surgical in-hospital care [7, 47]. The rehabilitation is focused on maintaining good nutritional status and the patients HRQOL [26, 27], which has been shown to correlate with the patient's physical status [6]. After a few years (approximately two-three years in Sweden) the patients are released into the primary care, as patients are considered "cured" from the follow-up care provided by specialist surgery clinic. The transition from follow-up by the specialist clinic into primary care has been identified as a vulnerable time for oesophageal cancer patients [48].

From the patient's perspective the post-operative course following oesophagectomy for cancer is experienced as significantly affecting the whole life situation, requiring major adaptations up to several years post treatment [49, 50]. The most affected aspect after treatment is the altered anatomy of the upper gastrointestinal tract, subsequently demanding changes to the patients eating habits [42, 50]. The first 12 months following the operation have been described in interview studies as "a period that had to be endured and survived" [51]. Further, during the first post-operative months, patients are heavily burdened by physical symptoms, e.g. vomiting, diarrhoea, weight loss, fatigue and dysphagia [25, 33, 52, 53]. The adjustment of eating habits and eating patterns has been described as dramatic and no longer associated with pleasure [50]. In addition, eating as a social activity has also been reported as embarrassing, with feelings of being stigmatised when eating [52]. Carey et al [42] even suggests that patients suffering from the consequences of oesophageal cancer treatment never fully adjust to the change in dietary practice that is required, after such an

extensive treatment. Subsequently, post-surgery dietary practice needs to be investigated further in order to generate an improved care model.

Additionally, the post-operative pathway has been thoroughly investigated with measures of HRQOL in this patient group. In brief, two months following the operation, patients self-reported HRQOL has been shown to be significantly reduced in all aspects measured (e.g., [symptom scales]; fatigue, nausea, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial problems and [function scales]; physical, role, emotional, cognitive, social and global health status) [54] by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) [55]. Further, six months after surgery, most aspects of quality of life are shown to be impaired among oesophageal cancer patients, as compared to a healthy reference population [56, 57]. No further improvements have been observed even after three years post treatment [56]. However, long-term survivors, e.g., surviving five years after treatment, have reported stable or improved HRQOL, as compared to assessments at six months post-operatively [58]. In contrast, patients surviving 10 years or more did not report improved HRQOL between five and 10 years. Instead, the patients' HRQOL deteriorated in almost all aspects, particularly role function and appetite loss. In addition, the same cohort of patients reported worse HRQOL, in particular more severe problems with reflux, eating difficulties, diarrhoea and appetite loss, as compared to a reference population. The impaired HRQOL is suggested to be related to the surgical reconstruction of the upper gastrointestinal tract, causing long-term anatomical and functional issues for the patients [59].

2.1.7 Differences in the course of treatment and follow-up between UK and Sweden

This thesis includes data from Sweden and England, UK. Therefore it is important to highlight some identified differences in the treatment pathway for patients diagnosed with oesophageal cancer who undergo treatment with curative intent. There are nearly 15 times more diagnosed cases of oesophageal (and cardia) cancer in the UK, than in Sweden (8,900 compared to 600) each year [1, 2]. The UK represents the country with the highest reported incidence of adenocarcinoma of the oesophagus worldwide and the majority of patients are white males [24] living in the most deprived areas [2]. However, male sex also represents the majority of patients diagnosed in Sweden [26] even though no association with living area has been reported. Differences in smoking habits and alcohol consumption between the countries have also been observed, with a higher consumption for the UK [60]. Further, the majority of patients diagnosed in the UK are 70 years old and above [36]. All patients aged

65 years and above are frequently pre-assessed by a special Older Persons Care Team at St Thomas' Hospital in London, where the English data included in this thesis were collected. No comparable team, aiming to identify risk patients among the older population of oesophageal cancer patients is available in Sweden [26]. Also, special cancer support groups including both carers and patients are more organised and incorporated within the UK health care system (e.g., [11, 12]). Moreover, to increase the hospital volume, hospital centralisation of surgery for oesophageal cancer has been implemented in Sweden and the UK, as well as the organisation of the treatment pathway by the collaboration in the MDT [26, 36]. However, in order to increase the quality and the use of the MDT, the UK has started a national educational program which has shown consistent quality improvements [61]. In addition, radical surgery remains the corner stone in the curatively intended pathway in both Sweden and the UK. However, both countries have implemented a combination treatment strategy of surgery together with neoadjuvant treatment for the majority of patients eligible for surgery during the past years, although chemotherapy is preferred in the UK and chemoradiotherapy is dominating in Sweden [26, 36]. The role of additional chemotherapy following the operation i.e., adjuvant chemotherapy has been suggested for a group of patients during the curative treatment pathway in the UK [62], but adjuvant therapy has no role in the Swedish treatment regime following oesophagectomy for cancer at present [26].

2.2 PSYCHOLOGICAL DISTRESS

2.2.1 What are emotions?

According to Tomkins [63, 64] and later Ekman and Rosenberg [65], we have nine basic emotions. Excitement, enjoyment and surprise are positive emotions, distress, fear, anger/rage, disgust, dissmell and shame are negative emotions. Emotions consist of a subjective component, a bodily representation, an “acting” mechanism, a cognitive process and a facial expression. They have an essential evolutionary role for humans by constituting our primary motivation, information and communication system i.e., an automated response system [66]. The response system analyses the current situation and motivates a behaviour to manage the situation [63].

A newborn has strong and immediate emotions, communicating essential needs to the parents, a fundamental survival strategy. However, during their lifetime an individual's expression of emotions i.e., the response system, is continuously adapted to the surrounding environment, significantly influenced by the individuals' social (including e.g., norms and

expectations), cultural and historical context. For example, in many contexts it is not seen as acceptable to cry when feeling sad (which in fact would be the adaptive response), and an individual then learns to repress this “real” and adaptive emotion by e.g., responding by replacing it with a different emotion (e.g., expressing maladaptive anger as opposed to the adaptive emotion sadness) or avoiding situations that are likely to lead to sadness. In another context, an individual may have learned that showing anger (e.g., saying “no” as a small child to an intimidating adult, i.e., an adaptive expression of the emotion anger) is dangerous and the better strategy is to respond by expressing sadness by crying or by “channeling” the adaptive feeling anger to be expressed as bodily symptoms (e.g., tension, headache, nausea).

It is important to note that much of these processes occur at an unconscious level [66].

In a given situation, when an individual comes into contact with one of these adaptive emotions, that have been learned to be avoided or defended against for some reason, it will trigger inhibitory emotions (e.g., anxiety, fear, shame), which in turn generates defence strategies such as the maladaptive expression of emotion (e.g., replacing one emotion with another) or other strategies (e.g., various bodily symptoms or avoidance behaviours) [66, 67]. This process of repressing adaptive emotions has conceptually been explained by Malan [68] and labelled the “Triangle of conflict” (Figure 1).

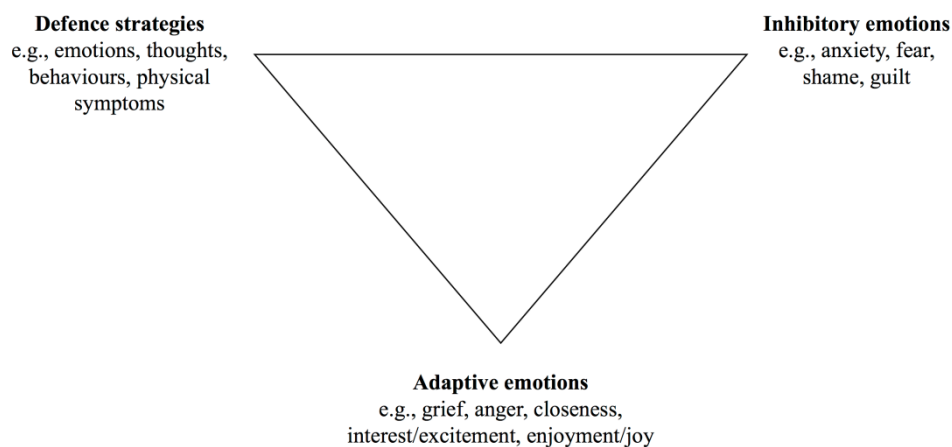


Figure 1. The triangle of conflict illustrating how repressed adaptive emotions (bottom corner) trigger inhibitory emotions (upper right corner) in turn generating various defence strategies (upper left corner).

To illustrate the triangle of conflict in the context of oesophageal cancer: Following oesophageal cancer surgery, a male patient suffers from rapid weight loss. Subsequently, the initial recovery phase is difficult and not as straightforward as the patient had imagined. The patient experiences fatigue, weakness, difficult eating situations, and subsequently his

nutritional status is poor. The patient's partner tries to convince him that he must eat, otherwise they have to be readmitted to hospital. The patient is under a lot of stress. He is well informed that good nutritional intake is a priority during the recovery phase. Thus, the eating situation is terrible, associated with pain, nausea, vomiting and diarrhoea. In facing eating situations and discussions with his partner he experiences increasing anxiety (i.e., an inhibitory emotion) which in turn leads to him avoiding these situations and expressing frustration and irritation towards his partner (i.e., defence strategies), even though he knows that his partner is only trying to care for him in the best way. In this hypothetical example, the repressed emotion is anger in the sense of the patient taking action or taking charge of his recovery. If the patient instead were able to express adaptive anger in the form of e.g., changing his behaviour by, for example, asking the dietician for help and including his partner in this process, it is likely that the irritation towards and avoidance of his partner as well as his distress (i.e., anxiety) would reduce.

It is important, however, to highlight the difference between adaptive coping strategies [69] and maladaptive responses and strategies developed to avoid and defend against expressing adaptive emotions [66]. Adaptive coping strategies are flexible strategies developed to reduce strong negative emotions (e.g., anxiety, grief or rage) in order to adapt to a given situation [69]. All individuals use a combination of maladaptive and adaptive responses. However, for the purpose of this thesis, it is important to distinguish between these different strategies, because an individual's defence strategy (adaptive or maladaptive) will have consequences for their psychological adaptation following a major life event e.g., severe illness.

2.2.2 Psychological distress in relation in cancer

2.2.2.1 The crisis reaction

Following a traumatic event e.g., a cancer diagnosis and treatment, an individual's mental capacity is mobilised in order to cope with the situation. The significance and the consequences of a trauma for each individual are determined by several factors. For example, the impact of the trauma (e.g., life threatening or not), the individual's life story and vulnerability, their present life situation, their social network and their personality including defence strategies in adaptive or maladaptive forms [70].



"Burdened by experience"

According to Cullberg [70] a “crisis reaction” can be described according to four different stages; shock, reaction, process/adaptation and reorientation. The first two stages, shock and reorientation constitute the acute crisis while the last two stages represent the adaptation process. The four stages, including differences in duration, characteristic behaviours and psychosomatic experiences, are summarised in Table 1.

Table 1. Schematic description of the four stages of crisis reaction adapted from Cullberg (2006).

<i>Acute crisis</i>			<i>Adaptation process</i>	
	STAGE 1: SHOCK	STAGE 2: REACTION	STAGE 3: PROCESS/ ADAPTATION	STAGE 4: REORIENTATION
Duration	Immediate – days	A few weeks	Six – 12 months following the traumatic event	12 months – ongoing
Characteristic behaviour	Inner chaos – outer calm Memory loss Acting out or numb	Mobilisation of defence strategies Repeatedly questioning – why?	Mentally processing the occurred	Reconciliation of the occurred
Psychosomatic experiences	Stress symptoms; e.g., poor sleep palpitation, diarrhoea		Physically adapt to the consequences of disease and treatment	

It is important to point out that a crisis reaction that progresses according to the four stages and is successfully processed by the individual will, most likely, lead to better psychological recovery in the long-term. However, several factors may interrupt the process. As regards to a cancer disease, it is important to mention that the course from diagnosis to “cured” might incorporate several “re-traumatising” events. For example, the diagnosis, the treatment, complications and a good prognosis that suddenly turns into a poor prognosis can all be considered “re-trauma” [70].

2.2.2.2 Anxiety

Anxiety is a response to a threatening event mediated by the somatic and autonomous nervous system, consequently causing biological, physiological and cognitive responses [67]. There are a range of anxiety syndromes and conditions [71], however, they are all characterised by intense worry and feelings of unease associated with an expected threatening

event. The distressing mental responses e.g., worry, fear, nervousness or even sudden panic, in combination with physical responses e.g., tension, restlessness, palpitation, sleep disturbance, are normal and essential reactions in relation to a sudden danger. The anxiety warns us and prepares us to avoid the situation. However, anxiety that is not associated with a traumatic event, or lasts for an extended time, causing suffering and hampers the individual's life, needs to be intervened [72].

2.2.2.3 Depression

Depression is defined as a mood disorder and involves a daily reduction in activity level, significantly impairing an individual's daily life function. The condition is characterised by sadness, loss of interest or pleasure, low self-worth and feelings of tiredness or a 'slowing down' and poor concentration. During this period the individual's sleep or appetite can be disturbed [73]. Depressed mood is experienced on a continuum from mild to severe [71]. Milder depression can be treated without medication and a moderate condition is recommended to be treated with medication and therapy. However, at its most severe, depression can lead to suicide [73, 74] and comorbidity of anxiety and depression is common [74].

In order to understand why some individuals may develop symptoms of psychological distress e.g., anxiety and depression, during the course of cancer treatment or later during recovery, it is important to consider both the typical progression of a crisis reaction and the unconscious mechanisms behind how repressed adaptive emotions trigger inhibitory emotions in turn generating defence strategies. This inner conflict of emotions has implications for an adaptive crisis reaction process. By repressing one emotion (e.g., anger) and replacing it with an alternative emotion (e.g., sadness), the progress through the crisis reaction process might become "locked" leading to unprocessed emotions thus triggering inhibitory emotions such as anxiety and responses such as depression.

2.2.2.4 Prevalence and predictors of anxiety and depression in cancer

It has been shown that cancer patients in general have double the risk of suffering from anxiety and depression, as compared to the general population [75]. However, prevalence rates of anxiety and depression differ greatly among cancer groups and are highly dependent on the screening instrument used, the psychometric properties of the instrument, the cancer population with regards to type, stage and treatment and the timing of the assessment [76-78]. The agreement between oncologists clinical assessment of emotional distress among cancer patients, as compared to patients self-report, have previously been considered low [79, 80] .

Complementary self-report instruments are quick, easy to administer, cost-effective and measure psychological and cognitive rather than physiological symptoms [77]. Moreover, a recent comprehensive meta-analysis including 211 research papers, comprising 238 cohorts and a total of 82,426 patients representing different cancer populations (i.e., breast, male genitalia, head and neck, haematological, female genitalia, digestive tract, respiratory tract, brain, skin, bone, soft-tissue, urinary tract and endocrine system) [81], compared prevalence rates of depression as measured by structured diagnostic interviews based on DSM-III/IV or ICD-10 criteria, or self-reports as measured by instruments with psychometric properties considered 'good' or 'excellent' [77] e.g., the Hospital Anxiety and Depression Scale (HADS) [82]. The results showed a combined prevalence rate for all cancer groups of 14% for major depression when measured by structured interviews, as compared to 18% when using the HADS, and 24% when using a different screening instrument. Further, varying prevalence rates across cancers groups were seen when using clinical interviews. For example, clinical depression was diagnosed in 3% of patients with lung cancer to 28% in patients with brain cancer. Regarding self-reports using the HADS, prevalence rates of depression ranged from 7% in patients with skin cancer to 31% in patients with cancer in the digestive tract. Overall, when measured by self-report, the acute phase (post-diagnosis) showed higher scores of depression (pooled prevalence rate 14%), as compared to measures during the first year of illness (9% combined rates) [81].

Regarding psychological distress, e.g., anxiety and depression combined, a large meta-analysis have shown a pooled prevalence rate of 32% for psychological distress, assessed by clinical interviews, among 1,448 cancer patients in different acute care hospitals [83]. Further, a meta-analysis based on 70 studies using clinical interviews when diagnosing probable anxiety or depression among 10,071 individuals from different oncological and palliative-care settings, at different time points, showed a combined prevalence rate of 10.3% for anxiety disorders and 19.2% for minor and 14.9% for major depression. However, when using a screening instrument for anxiety and depression (i.e., Psychosocial screen for Cancer Questionnaire) among 10,153 cancer patients after diagnosis but prior to treatment, the combined prevalence rate was 19% for anxiety across cancer groups and 13% for depression. The highest mean scores of anxiety and depression were seen in gynaecologic and hematologic cancer groups, as compared to skin and prostate cancer. Female sex and younger age, compared with males and older age, were predictors of increased psychological distress [84].

2.2.3 Psychological distress and oesophageal cancer

The overall prognosis of oesophageal cancer remains poor. However during recent years advances in the curative treatment regime have increased survival rates following curatively intended treatment [85]. Consequently, the number of oesophageal cancer survivors will increase during the coming years. Previously, the literature investigating psychological distress in oesophageal cancer has been sparse and representative studies have been called for [9]. To date, a significant increase in anxiety and depression scores, as measured by the HADS has been observed in oesophageal cancer patients two years post-diagnosis. Of 484 included patients, 36% met the criteria for probable anxiety and 24% met the criteria for probable depression. Younger age and patients without a 'carer' were predictors of anxiety. Patients with comorbid physical diseases were more likely to report depression. However, when controlling for all these factors in the multivariable regression model, coping variables and illness perceptions were more likely to explain the variance of psychological distress [11]. Further, in a longitudinal study, with a smaller sample size (n=90) including patients treated with both palliative and curative intent, 42% of the patients reported probable or possible anxiety disorder and/or depression disorder not at diagnosis but prior to treatment, measured by the HADS. Patients were subsequently followed up at one, two, three, six- and 12 months post-diagnosis. However, no statistically significant changes were observed over time for the HADS total score i.e., anxiety and depression scales combined. However, the scores on the depression scale alone on the HADS increased during the first six months. In addition, at inclusion (prior to treatment) anxiety and depression were observed to be highly comorbid conditions, with 73% of patients reporting overlapping symptoms. Further, increased anxiety at diagnosis was associated with the duration of tumour related symptoms pre-diagnosis and later also at the one- and six month follow-up. Female patients were more likely to report anxiety at the early follow up (at one, two, and three months post-diagnosis) than male patients [13].

Moreover, in a large Swedish cohort study including 1,615 patients who underwent surgery for oesophageal cancer, new onset psychiatric morbidity, defined as psychiatric in- or outpatient care or prescription of psychotropic drugs and measured with two-year cumulative incidence, was observed in 2.5% (in-patient care), 4.2% (outpatient care) and 32.2% (treatment with psychotropic drugs) of the population. The occurrence of psychiatric disorders was also higher in the patient group as compared to the Swedish background population. In addition, after adjustment for known prognostic factors, new-onset psychiatric morbidity was associated with poorer survival in the specified cohort [10]. In a recent, register based study

carried out in the UK, 1,029 patients who had undergone oesophagectomy or gastrectomy, two years earlier were included. Within 12 months of surgery, 12.5% of the patients were recorded as having either a diagnosis code or a prescription code for treatment for psychiatric illness. Almost all patients (98%) with postoperative psychiatric morbidity were diagnosed with anxiety or depression. Moreover, younger age, preoperative psychiatric morbidity and 30-day complications were variables associated with increased risk of anxiety or depression following the operation. However, after adjustment for several confounding factors, at least one postoperative symptom was independently associated with post-surgery anxiety or depression. Importantly, pain, dumping and loss of appetite were reported as the independently most impacting symptoms (yet, not statistically significant) on post-operative anxiety and depression (Odds Ratio [OR 4.42 pain; OR 3.38 dumping; OR 2.66 loss of appetite) [86].

There are five main reasons why patients with oesophageal cancer may represent a particularly vulnerable patient group when it comes to psychological distress following diagnosis and treatment. These five reasons are: a) the vital function of the oesophagus, b) the symbolic value of eating, c) the severe treatment pathway, d) the demanding recovery process and e) the poor prognosis. Considering these reasons and the additional statement that few people would rather choose to die than undergo curatively intended treatment, despite the severe treatment regime and no offer of a second line treatment, it is clear that oesophageal cancer patients are exposed to a vastly psychologically challenging time from diagnosis and onwards. This leads to the questions such as, do these challenges impact on the patient's ability to recovery and to what extent?

3 THESIS AIMS

The overarching aim of this thesis was to describe the psychological distress experienced by oesophageal cancer patients from time of diagnosis up to five years following curatively intended surgery. This was addressed using the following four research questions:

- 1) What is the symptom severity and prevalence of anxiety and depression among surgically treated oesophageal cancer patients from diagnosis up to 12 months post-operatively?
- 2) Are there any risk factors that are predictive of increased psychological distress from diagnosis to 12 months after surgery?
- 3) Are aspects of emotional functioning, including tension, worry, irritation and depressed mood, negatively affected at six months and five years post-surgery, and what are the risk factors for problems on the four aspects?
- 4) How do patients' narratives describe their adaptation from diagnosis to six months post-operatively when interviewed at six months following surgery?

4 MATERIALS AND METHODS

4.1 OVERVIEW

An overview of the materials and methods used in Studies I-IV included in this thesis is provided in Table 2.

Table 2. Materials and methods for studies I-IV.

	Study I	Study II	Study III	Study IV
Design	Cross sectional study	Cohort study	Cohort study	Qualitative interview study
Data source	STH	STH	SECC	Patient narratives
Study time	Pre-surgery	Pre-surgery, six and 12 months post-surgery	Six months and five years post-surgery	Six months post-surgery
Outcome	Anxiety and depression	Anxiety and depression	Emotional functioning; tension, worry, irritation, depressed mood	Patient experiences
Outcome measure	HADS	HADS	EORTC QLQ-C30	Unstructured interviews
Risk characteristics – Clinical	Age, sex, activity status, tumour histology, tumour stage, neo-adjuvant treatment	Age, sex, in-hospital complications, activity status, dysphagia, tumour histology, tumour stage, neo-adjuvant treatment, adjuvant treatment, recurrence	Age, sex, tumour histology, tumour stage	
Risk characteristics – Sociodemographic	Education, cohabitation, work status	University degree, cohabitation, work status	Marital status, education level	
Analysis	Multivariable logistic regression	Mixed effects modelling	Multivariable logistic regression	Qualitative content analysis

Note: STH=St Thomas' Hospital, SECC=Swedish Esophageal and Cardia Cancer database, HADS=Hospital Anxiety and Depression Scale, EORTC QLQ-C30=The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30

4.2 DATA SOURCES

4.2.1 St Thomas' Hospital Cohort

Data from a prospective hospital-based cohort study carried out at St Thomas' Hospital (STH) in London, England, between November 2011 and March 2016 was used in **Studies I** and **II**. The STH is a high volume centre for oesophageal cancer surgery with approximately 150 cases operated yearly. Therefore, following a diagnosis at, or referral to STH for curatively intended oesophageal resection, patients were identified by a research coordinator for inclusion in the clinical cohort. Upon admission to the upper gastrointestinal inpatient ward, the study was explained to the patients who were invited to take part. If patients agreed to participate, written informed consent was obtained at this time point. The database incorporates both clinical data and patient-reported outcome measures (PROM). The clinical data collection includes pre-surgical assessments of the patients, surgical and medical information collected in theatre during the operation and post-operative information collected during the patients post-operative in-hospital stay. The clinical information was obtained from two research coordinators who followed the patients from admission to the upper gastrointestinal inpatient ward through to discharge. The standard curative treatment pathway for resectable tumours at STH is elective surgery in combination with six cycles of chemotherapy in total (i.e., three cycles of neo-adjuvant and three cycles of adjuvant chemotherapy. If a positive resection margin is reported after surgery (i.e., microscopic tumour cells in the resection margin), an addition of chemo radiotherapy (CRT) is recommended, for disease control. Further, due to neoadjuvant treatment the median time between diagnosis and surgery is approximately 147 days, for patients treated at STH. Patients were asked to complete the PROM assessment by the research coordinators on the day before surgery (baseline) and subsequently at six and 12 months post-surgery. The follow-up PROM was sent to patients' homes to be completed and returned by post. Ethical approval for the clinical database was obtained from the National Research Ethics Service London Bridge (REC 11/LO/0335) whereas the PROM assessment was granted ethical approval by the West Midlands research ethics committee (REC 13/WM/0131).

4.2.1.1 Clinical variables

All clinical variables available in the STH database were prospectively collected, by a research coordinator according to a pre-defined study protocol, in collaboration with the MDT consisting of oncologists, pathologists, surgeons, dieticians and contact nurses. The patients' medical records were also retrieved from other hospital units and made available during the in-hospital stay and relevant data were gathered from these records. For the

purpose of **Study I** age, sex tumour histology, tumour stage (according to UICC 7th edition [87]) and neo-adjuvant treatment status were used as predictor variables. In **Study II** the above-mentioned clinical variables were included together with complementary information on in-hospital complications and tumour recurrence.

4.2.1.2 PROM assessment and socio-demographic variables

A self-report questionnaire battery was administered to the patients at baseline and then at 6 months and 1 year following surgery. The baseline measures were completed by the patients on the day before oesophageal cancer surgery. The follow-up questionnaires were posted to the patients' home, to be filled in and returned by post. Two reminder letters were sent out when necessary. In **Study I** self-reported education level, cohabitation, activity and work status were used as predictor variables. In **Study II** self-reported dysphagia was used as a predictor variable in addition to self-reported education level, cohabitation, activity and work status as in study I.

4.2.1.3 Anxiety and depression

Anxiety and depression were used as outcome variables in **Studies I** and **II**, measured by the HADS [82], incorporated in the larger PROM assessment in the data collection. Anxiety was defined as scores of 8 or above on the HADS reflecting feelings of restlessness or tension, with continuous thoughts of fear, worry or sudden panic. Depression was defined as scores of 8 or above on the HADS questionnaire reflecting a sense of feeling 'slowed down' or low functioning and a general loss of interest and inability to feel pleased. Importantly, both anxiety and depression are associated with limitations in the patient's daily life, for example limited activity status and self-expressed suffering [71]. The HADS is a brief questionnaire developed to measure anxiety and depression in cancer patients in hospital settings. Although it has been widely used and validated for this purpose, as a brief screening instrument in the clinical oncology setting, for clinical oncology use [90], it is important to note that it is not comparable with a diagnostic interview [81, 89]. The HADS includes 14 items on two dimensions with seven items corresponding to anxiety ('anxiety subscale') and seven corresponding to depression ('depression subscale'). Items are scored from 0 to 3 generating a total score ranging from 0 to 21 on each subscale, with higher scores reflecting more severe symptoms. According to the scoring manual [90], established cut-off scores for each subscale are: 0-7 normal status (i.e., no anxiety or depression), 8-10 mild symptoms of anxiety or depression, 11-14 moderate symptoms of anxiety or depression, and 15-21 severe anxiety or depression symptoms. Scores for mild symptoms (8-10) correspond to possible 'caseness' of

anxiety or depression disorder whereas scores of 11 and above indicate probable ‘caseness’ of anxiety or depression disorder.

4.2.2 Swedish Esophageal and Cardia Cancer database

The Swedish Oesophageal and Cardia Cancer database (SECC) was used in **Study III**. The SECC is a cohort study including surgically treated oesophageal- and cardia cancer patients in Sweden between April 2nd 2001 and December 31st 2005. The database is prospective in design and incorporates 90% of all patients who had been operated for oesophageal cancer during the given time period. Patients were identified through a nationwide network of hospital departments and clinicians at 174 hospitals in Sweden, who were involved in the management of the patients with cancer in the oesophagus or the cardia. Both clinical and socio-demographic variables are available in the SECC database. Clinical variables were retrieved from a prospective extraction of data from medical records from histopathological, endoscopic and surgical units according to a pre-defined study protocol and carried out by medical researchers at Karolinska Institutet. Socio-demographic variables were available through register linkage with the nationwide Swedish Population and Housing Census and the longitudinal integration database for health insurance and labour market studies (LISA), held by Statistics Sweden [91]. In addition, patients were followed up with assessments of HRQOL at six months and five years post-surgery. The database obtained ethical approval from the Regional Ethical Review Board in Stockholm, Sweden DNR 01-064 with amendments 01-340, 05/1491-32 and 2012/712-32.

4.2.2.1 Clinical variables

For the purpose of **Study III**, the clinical variables age, sex, tumour histology and stage were used as predictor variables. These were prospectively collected by the extensive review of medical records from the surgical, endoscopic and pathology units at each hospital who contributed to the data collection, as described above. Tumours near the gastro-oesophageal junction were classified according to Siewert’s definition [92]. Tumour stage was classified according to the International Union Against Cancer 6th edition [93].

4.2.2.2 Socio-demographic variables

For the purpose of Study III, information on education level and marital status was retrieved through record linkage with the nationwide registry LISA [91] and collected for each patient as close to the date of operation as possible. Individual record linkage between the SECC database and LISA was enabled by the means of the unique personal identity number assigned to all Swedish residents.

4.2.2.3 *Aspects of emotional functioning*

Aspects of emotional functioning were used as outcome measure in **Study III** and defined as tension, worry, irritation and depressed mood drawn from the emotional functioning scale (items 21-24) within the EORTC QLQ-C30 [55]. The questionnaires were sent to the patients' homes, to be completed and returned by post, at six months and five years following curatively indented surgery. Up to three reminders were sent out to the patients if necessary. The EORTC QLQ-C30 is a cancer specific questionnaire and widely used when assessing HRQOL in patients with cancer, with good validity and reliability [55]. The questionnaire consists of 30 questions incorporating five functioning scales, three symptom scales and six single items. For the purpose of study III, only the emotional functioning scale was used, as a proxy for anxiety and depression. The emotional functioning scale consists of four targeted questions assessing tension ("did you feel tense"), worry ("did you worry"), irritation ("did you feel irritable"), and depressed mood ("did you feel depressed") during the past week. Each item is scored on a four-point scale; 1) "not at all", 2) "a little", 3) "quite a bit", and 4) "very much". High scores on the functioning scale correspond to better emotional function and conversely, low scores indicate poorer emotional functioning [94]. Notably, when screening for symptoms of anxiety and depression in different cancer groups, the overlap between the emotional functioning scale on the EORTC QLQ-C30 and the HADS has repeatedly been shown [95-97]. Significant correlations ($p < 0.001$) have been shown for all 14 items of the HADS and the four items incorporating the emotional functioning scale. However, the HADS anxiety subscale showed a stronger association with the four aspects, as compared with the HADS depression subscale. The highest correlations have been shown for the anxiety subscale and items measuring tension, worry and depression mood [95].

4.2.2.4 *Comparison with a Swedish reference population*

A random sample of 6,969 adults was invited to complete an HRQOL assessment using the EORTC QLQ-C30 questionnaire, in order to collect reference values from the Swedish background population. This reference population was generated in response to the lack of disease free baseline values in studies of oesophageal cancer (i.e., for use as "proxy" baseline values). Participants, aged 40 to 79 years were frequency matched on age and sex to mirror the characteristics of the patients included in the SECC database. The questionnaires were sent to participants' homes, to be completed and returned by post, at one time point. One reminder was sent out if necessary. For the purpose of **Study III**, a comparison between this Swedish reference population and patients at six months and five years in the SECC database was used regarding emotional functioning i.e., items assessing problems with tension, worry,

irritation and depressed mood, on the EORTC QLQ-C30 to assess whether the proportions of problems with aspects of emotional functioning observed in patients following oesophageal cancer surgery were higher than the proportion of problems in the Swedish background population.

4.2.3 Qualitative data collection

Between 1st of November and the 31st of December 2016, a qualitative data collection with in-depth interviews was carried out and used to address the aim of **Study IV**. Patients, who had been operated for oesophageal cancer approximately six months prior to 1st November 2016, were identified via two specialised upper gastrointestinal clinics in Sweden, Uppsala University Hospital and Skåne University Hospital. Almost all patients at these two centres, who fulfilled the inclusion criteria, were asked for participation. Inclusion criteria were patients who had undergone curatively intended resection for oesophageal cancer six months earlier and who consented to participate in the interview study. Patients suffering from a disease recurrence were not considered eligible for the study. Due to low numbers of yearly cases undergoing oesophagectomy for cancer in Sweden [5] almost all patients were asked for participation. The selected time window (i.e., six months post-operatively) was chosen due to earlier studies indicating that patients suffer reduced HRQOL and could be in need of additional support at this time point [57, 98]. In addition, the patients' ability to put into words their experiences of the disease and treatment might be reasonable at this time point [70]. After identification through the upper gastrointestinal clinics, a letter describing the full details of the study was sent to patients' home. Patients, who did not want to be contacted, regarding participation in the study, were asked to decline study participation through e-mail, post or telephone within two weeks. Patients, who did not decline study participation at this time, were contacted via telephone by the interviewer. During the phone call, full information about the aim and study procedure was provided and if the patient agreed to participate, a time and place for the interview was decided. Further, all interviews were conducted in the patients' home, except for one which took place at Uppsala University. Before the start of each interview, the study was once more fully described and written informed consent was retrieved from the participants. The in-depth face-to-face interviews were tape-recorded and ranged from 32 to 54 minutes (median time: 46 minutes). A pre-defined interview guide including themes that reflected the chronological order from diagnosis to present day were used in order to follow the same structure throughout all interviews and mirrors the study aim. However, open-ended questions were used throughout all interviews and follow-up questions ("prompt questions" e.g., can you tell me more; can you explain in more detail)

were asked in order to increase the richness of the data. The interviews were conducted by the thesis author, a registered nurse, with a clinical background in palliative care and with an additional degree in psychotherapy, trained to have conversations with patients suffering from an advanced disease. Ethical approval was obtained from the Regional Ethical Review Board in Uppsala, Sweden (DNR 2016/199).

4.3 STATISTICAL ANALYSES

The statistical analyses were carried out using SPSS for Windows (version 21, Chicago, IL, USA) in **studies I** and **II** or SAS (version 9.2, SAS Institute Inc, Cary, NC) in **Study III**. P-values <0.05 were considered statistically significant.

4.3.1 Psychometric properties of the HADS

To assess the performance and dimensional structure (i.e., psychometric properties) of the HADS in this study population, a principal component analysis (PCA) was conducted [99]. The number of factors retained for extraction and rotation was based on the Kaiser criterion (eigenvalues >1) and visual inspection of the scree plot. Oblique rotation, with direct oblimin method ($\delta=0$) was used to explore the retained factors, as factors were assumed to correlate. Items loading 0.40 or lower were suppressed to aid interpretation of the factors [100]. Internal consistency was assessed by means of Cronbach's alpha coefficients.

4.3.2 Descriptive statistics

Standard descriptive statistics were calculated to present the information on clinical and sociodemographic variables obtained from the samples included in the four studies (**Studies I – IV**) and shown as means and standard deviations (SD) for numeric variables and as numbers (n) and percentages (%) for categorical variables.

4.3.2.1 Studies I and II

The prevalence of anxiety and depression as measured by the HADS was calculated using the established cut-offs (i.e., scores ≥ 8 on each subscale) indicating cases of 'possible-probable' anxiety or depression disorder in **Studies I** and **II**. Symptom severity, i.e., total scores on the HADS sub-scales of anxiety and depression were presented as means and SDs. In addition, four mutually exclusive groups describing potential symptom overlap were created and included in the analyses in **Study I**. Based on scores ≥ 8 on each subscale, patients were defined as reporting 'anxiety only' (no depression), 'depression only' (no anxiety), 'co-morbid anxiety and depression' (both anxiety and depression) or 'symptom free' (i.e., no anxiety and no depression).

4.3.2.2 *Study III*

In **Study III**, patients were defined as reporting ‘no problems’ for scores of 1 on any of the four individual items that were included to represent aspects of emotional functioning (i.e., tension, worry, irritation and depressed mood) from the emotional functioning scale (items 21-24) on the EORTC QLQ-C30. Patients scoring ≥ 2 on any of these items were defined as reporting ‘problems’ on aspects of emotional functioning.

4.3.3 Differences between responders and non-responders

To assess whether non-responders differed in any way from responders on clinical and sociodemographic variables, Pearson’s Chi-squared test (or Fishers Exact test when numbers were small in cells) was used in **Studies I – III**.

4.3.4 Comparison with a Swedish reference population

To compare whether the proportion of problems observed on aspects of emotional functioning (i.e., tension, worry, irritation and depressed mood) was higher among patients following oesophageal cancer surgery than the proportion of problems observed on aspects of emotional functioning in a random sample from the background population, incidence rate ratios (IRR) were calculated. The IRR is the estimated rate ratio comparing the SECC patients to the background population sample, adjusting for age, sex, marital status and education. IRRs were calculated both for six months and five years.

4.3.5 Multivariable logistic regression models

4.3.5.1 *Studies I and III*

Multivariable logistic regression models, with odds ratios (OR) and 95% confidence intervals (CI) were used for the analyses carried out in **Studies I** and **III** to examine the association between clinical and sociodemographic variables and anxiety and depression (**Study I**) and problems with aspects of emotional functioning, that is, tension, worry, irritation and depressed mood (**Study III**). The model calculated in **Study I** included information on age (<65 years or ≥ 65), sex (male or female), education (elementary school [<12 years of education] or university degree [≥ 12 years of education]), cohabitation (non-cohabitating or cohabitating), activity status (no limitations or limitations) and work status (working or not working). In an additional analysis, anxiety and depression were included as variables in the models to account for the influence of possible comorbid anxiety and depression on the outcomes (i.e., anxiety and depression). The model calculated in **Study III** included information on age (<60 years, 60–74 years, or ≥ 75 years), sex (male or female), tumour

stage (0–1, II, or III–IV) tumour histology (adenocarcinoma or squamous cell carcinoma), education (nine-year compulsory schooling, upper secondary schooling, or higher education) and marital status (non-cohabitating [never married or widowed/divorced] or cohabitating [married or remarried]).

4.3.6 Mixed-effects model

4.3.6.1 Study II

Potential changes in anxiety and depression over time (i.e., from pre-surgery to 12 months after surgery) and the association between clinical and sociodemographic variables and anxiety and depression were examined using a mixed-effects model, with maximum likelihood estimation, including random intercepts and slopes, in **Study II**. The model accounted for the categorical variables time (pre-surgery, six-month follow-up or 12-month follow-up), age (<65 years or ≥65 years), sex (male or female), university degree (yes or no), cohabitation (living alone or cohabitating), in-hospital complications (yes or no) and tumour histology (adenocarcinoma or squamous cell carcinoma). Continuous variables included in the model were scores on activity status and dysphagia from pre-surgery to 12 months after surgery.

4.3.7 Missing data on outcome measures

4.3.7.1 Studies I and II

According to the scoring manual for the HADS [90], missing data should be handled as follows; if one item is missing on either of the subscales, the score on this single item should be inferred from the mean score of the remaining six items for which there are no missing data. In **Study I**, three patients had one missing item on the HADS anxiety subscale at the pre-operative assessment. In line with the recommendations, an imputation of the mean from the remaining six items was carried out. There were no missing data on the HADS depression subscale in study I. In **Study II**, four patients had one missing item on the HADS anxiety subscale at the pre-operative assessment, one patient had one missing item on the HADS anxiety subscale at the six- and 12-month follow-up assessments. One patient had one missing item on the HADS depression subscale at the pre-operative and six-month assessments. These missing values were imputed according to the recommendations described above.

4.3.7.2 *Study III*

Patients with missing data on any of the EORTC QLQ-C30 items 21-24 were excluded from the analyses carried out in **Study III**, as per the instructions in the scoring manual [94]. One patient had missing data on the item assessing depressed mood at six months after surgery and was excluded. At the 5-year follow-up assessment, one patient had missing data on the item assessing worry and was excluded from the analyses.

4.4 QUALITATIVE ANALYSIS

4.4.1 Qualitative content analysis

For the purpose of **Study IV**, an overarching inductive framework was used throughout the analysis process, meaning that different empirical parts from the interviews were brought together as a whole in order to enrich the empiric material [101]. Data were analysed using qualitative content analysis, as described by Graneheim and Lundman [102]. The analysis process was characterised by a continuous movement, back and forth, during all steps along the analysis process. A trained transcriber, outside of involvement in the data collection, transcribed all the interviews verbatim. Two different people (the thesis author and an associate professor in clinical psychology) conducted the analysis in parallel, in an attempt to obtain objectivity during the analysis process. Following the transcription, the material was read through several times, applying a naïve understanding. Meaning units were separately identified and condensed. In the next step, the condensed meaning units were labelled with a code and compared based on differences and similarities. The process thus far was made on a manifest level, close to the text. Following the initial coding, the remaining four co-authors (three nurses and one oesophageal cancer surgeon) participated in the creation of categories. Separately, all co-authors created categories which were then compared, discussed and revised. This process resulted in the identification of 14 sub-categories. Three categories were created based on the codes that shared the same content and this still represented the manifest content of the text. Finally, one theme emerged, as a ‘red thread’ throughout the whole material, representing the latent interpretation of the patient narratives. Representative quotations were chosen to illustrate the research findings [103].

4.5 ETHICAL CONSIDERATIONS

All studies included in the thesis were granted ethical approval and informed consent was obtained from all study participants. Prior to the consent, forms were signed by the participants, full details were given verbally and in written text, notifying that participation in a given study was voluntary and the individuals were allowed to withdraw at any time along

the way. All participants also had the opportunity to ask additional questions about the given study, at this time point. However, it cannot be ignored that the studies included in this thesis were conducted during a vulnerable time, in a patient group that is experiencing a great deal of distress. In addition, due to the fatal nature of the disease, patients diagnosed with oesophageal cancer are prioritised within both medical and HRQOL research contexts, and consequently are, asked to voluntarily participate in many different studies at the same time, along the treatment trajectory in both England and Sweden. However, it is also important to address that patients desire to take part in research in order to improve the care not only for themselves but also for other patients, by sharing their perspective of being a patient and contributing to clinical data collections. In addition, some extra attention regarding ethical considerations in **Study IV**, the qualitative interview study needs to be addressed.

Conducting in-depth interviews where participants are invited to reflect upon a newly experienced frightening situation might evoke strong emotional reactions and feelings that are perceived as deeply uncomfortable, for the participant. Moreover, when sharing difficult experiences, the risk that the participant is left in a psychologically distressing condition that is not expected or wanted, must be considered. The author of this thesis, who also conducted all interviews in study IV, is a registered nurse with a clinical background in palliative care and a psychotherapist, experienced and trained in handling difficult conversations and evaluating psychological responses when talking about challenging experiences. Importantly, sharing a perspective and putting into words these experiences together with a person who is interested in their lived experience can also be restorative for the patients.

5 RESULTS

5.1 PATIENT OVERVIEW

Final patient numbers as well as clinical and sociodemographic characteristics of all patients included in **Studies I – IV** are summarised in Table 3. Further, a higher proportion of patients diagnosed with squamous cell carcinoma and a lower tumour stage was observed for non-responders in **Study I**, as compared with responders. In **Study II**, the responders had a higher proportion of in-hospital complications at six months post-surgery, as compared to non-responders. No statistically significant differences were observed between responders and non-responders in **Study III**.

5.2 ANXIETY AND DEPRESSION

5.2.1 Psychometric properties of the HADS

The PCA revealed a two-factor structure explaining 56.86% of the variance. The rotated factor structure found the anxiety items of the HADS loading satisfactorily onto the first factor, and the depression items loading satisfactorily on the second factor. However, item 7 ‘I can sit at ease and feel relaxed’, loaded highly on both factors, as has been observed previously [104]. Cronbach’s alphas were 0.89 for the anxiety subscale and 0.83 for the depression subscale, indicating satisfactory internal consistency [105].

5.2.2 Anxiety and depression prior to surgery

5.2.2.1 Study I

In **Study I**, 122 patients underwent curatively intended surgery for oesophageal cancer during the study period. Of these, 106 patients (87%) were included in the study. Prior to surgery 36 patients (34%) scored above the clinical threshold (≥ 8) for anxiety. Sixteen (15%) had scores indicating mild anxiety, 15 (14%) reported moderate anxiety and five (5%) had scores indicating severe anxiety. On the depression subscale of the HADS, 24 (23%) patients reported symptoms above the cut-off (≥ 8), 16 (15%) reported mild symptoms, five (5%) had scores indicating moderate symptoms and three (3%) had severe symptoms of depression. Almost half of the patients (45 [42%]) were symptomatic, meaning that they reported anxiety and/or depression and 15 patients (14%) reported overlapping symptoms of anxiety and depression. However, the majority (61 [58%]) were symptom free prior to surgery (figure 2). The mean symptom score on the anxiety subscale was 5.78 (SD 4.62) and the mean symptom score on the depression subscale was 4.19 (SD 3.92).

Table 3. Overview of patient characteristics in Studies I – IV.

	Study I*	Study II**	Study III***	Study IV
Number of patients	106	218	401	10
Sex				
Male	81 (76)	178 (82)	326 (81)	8 (80)
Female	25 (24)	40 (18)	75 (19)	2 (20)
Age, mean (SD)		63.94 (9.86)	--	
Age				
<65	50 (47)	102 (47)	--	
≥65	56 (53)	116 (53)	--	
<60	--	--	101 (25)	--
60 – 74	--	--	231 (58)	--
≥75	--	--	69 (17)	--
Education				
University degree		36 (17)		
Not university degree		178 (82)		
<7 years	7 (7)	--		
7 – 12 years	56 (53)	--		
>12 years	40 (38)	--		
Nine-year compulsory	--	--	183 (46)	
Upper secondary	--	--	153 (39)	
Higher education	--	--	58 (15)	
Cohabitation status				
Living alone	26 (25)	43 (20)	133 (34)	
Cohabiting	76 (72)	164 (75)	264 (66)	
Working at time of diagnosis				
Yes	45 (42)	93 (43)		
No	61 (57)	125 (57)		
Tumor histology				
Adenocarcinoma	95 (90)	204 (94)	303 (76)	
Squamous cell carcinoma	11 (10)	14 (6)	98 (24)	
TNM stage				
I	4 (4)	9 (4)	84 (21)	
II	--	58 (27)	120 (30)	
Ila	18 (17)	--	--	
IIb	9 (8)	--	--	
III	72 (68)	144 (66)	160 (40)	
IV	1 (1)	2 (1)	33 (9)	
Unable to assess	1 (1)	--	--	
Neoadjuvant treatment				
Yes	91 (86)	183 (84)		
No	12 (11)	23 (11)		
Not known	--	12 (5)		
Adjuvant treatment				
Yes	--	115 (52)		
No	--	71 (33)		
Not known	--	32 (15)		
In-hospital complications				
Yes	--	106 (49)		
No	--	112 (51)		
Tumour recurrence				
Yes	--	49 (23)		
No	--	164 (75)		
Not known	--	5 (2)		

Missing data: *Education n=3, cohabitation status n=4, tumor stage n=1, neo-adjuvant treatment n=3, working n=1.

**university degree n=4; cohabitation, n=11; working at diagnosis n=1; TNM stage n=5.

***Missing data: tumour stage n=4, marital status n=4 and education level n=7.

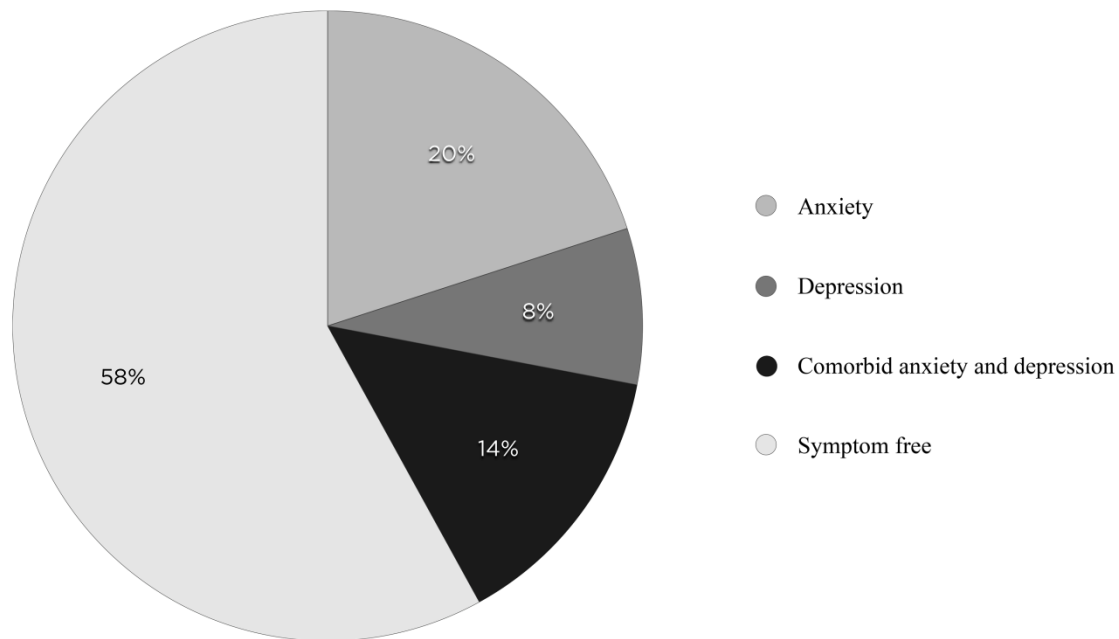


Figure 2. Proportion of anxiety, depression, comorbid symptoms and no symptoms of anxiety and depression prior to surgery.

5.2.3 The course of anxiety and depression from pre-surgery to 12 months post-surgery

5.2.3.1 Study II

During the study period, 260 patients were treated with surgery for oesophageal cancer, of whom 218 (83%) were included in the pre-surgical assessment in **study II**. Prior to surgery 72 patients (33%) reported symptoms of anxiety and 44 patients (20%) reported symptoms above the cut-off (≥ 8) on the depression scale on the HADS (Figure 3). In addition, comorbid symptoms of anxiety and depression were reported in 31 patients (14%). At six months post-surgery, 178 patients (68%) were eligible for follow up, of these, 139 patients (78%) completed the PROM assessment. At 12 months, 129 patients (93%) were eligible for inclusion; of these 95 (74%) filled in the PROM assessment. Co-morbid symptoms of anxiety and depression were seen in 18% of the patients at 6 months and in 28% at 12 months.

The proportion of reported symptoms above the cut-off on the anxiety sub-scale in **Study II** showed that 33% of the patients reported anxiety prior to surgery, remaining in the vast majority of the patients at six months (28%) and increasing to 37% of the patients at 12 months post-surgery. The unadjusted mean scores on the HADS anxiety scale were 5.64 (SD 4.48) prior to surgery, 5.43 (SD 4.76) at six months and 5.60 (SD 4.71) at 12 months post-

surgery. Although the proportion of patients with anxiety appeared to increase, when running the mixed-effect model, adjusting for clinical and socio-demographic variables, the adjusted mean scores across time-points remained stable, and did not significantly change over time ($\beta = -0.21$, 95% CI -0.65 to 0.23 , $p = 0.349$ (Figure 3).

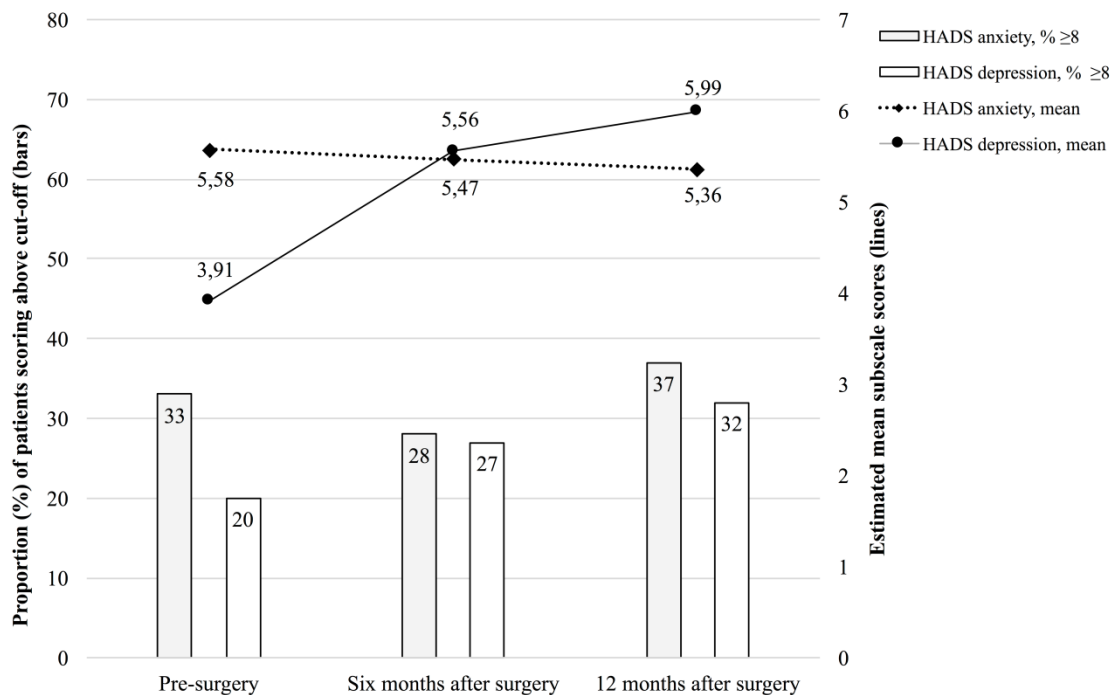


Figure 3. Anxiety and depression at pre-surgery, six months and 12 months after surgery shown as proportions above cut-off and estimated mean scores.

The percentages of patients scoring above the clinical threshold for possible-probable depression disorder were 20% prior to surgery, 27% at six months and 32% of the patients at 12-months. The unadjusted mean scores for the HADS depression sub-scale were 3.91 (SD 3.67), 5.65 (SD 4.48) and 5.53 (SD 4.73), at the three time points, respectively. Although depression appeared to increase over time, when including clinical and socio-demographic variables in the mixed-effect model for depression, no statistically significant increase in depression symptoms over time was observed (time: $\beta = 0.64$, 95% CI -0.44 to 1.72 , $p = 0.243$; time squared: $\beta = 0.02$, 95% CI -0.53 to 0.57 , $p = 0.931$).

5.2.4 Potential risk factors for anxiety and depression

5.2.4.1 Study I

In **Study I**, prior to oesophageal cancer surgery, women were significantly more likely to report anxiety symptoms above the cut-off than men (OR 4.04, 95% CI 1.47-11.17), when adjusting for age, education, cohabitation, activity status and work status. However, depression was associated with patients reporting limitations in their activity status (OR 6.07, 95% CI 1.53-24.10), as compared to those reporting no limitations, after adjustment for clinical and sociodemographic variables. Further, when accounting for the influence of possible comorbid anxiety and depression, these results remained (female sex OR 5.14, 95% CI 1.66-15.90 and limitations in activity status OR 6.21, 95% CI 1.48-26.10, for anxiety and depression, respectively).

5.2.4.2 Study II

After accounting for the influence of time and other clinical and socio-demographic variables included in **Study II**, younger age ($\beta = -1.78$, 95% CI -2.81 to -0.74 , $p = 0.001$), female sex ($\beta = 1.73$, 95% CI 0.32 to 3.14 , $p = 0.016$), living alone ($\beta = -1.33$, 95% CI -2.61 to -0.06 , $p = 0.041$), greater limitations in activity status ($\beta = 0.69$, 95% CI 0.19 to 1.19 , $p = 0.007$) and more severe self-reported dysphagia ($\beta = 0.02$, 95% CI 0.001 to 0.04 , $p = 0.033$) remained as significant risk factors for higher anxiety symptoms. Moreover, statistically significant risk factors for higher depression scores were in-hospital complications ($\beta = -0.94$, 95% CI -1.74 to -0.14 , $p = 0.021$), greater limitations in activity status ($\beta = 2.13$, 95% CI 1.71 to 2.56 , $p < 0.001$) and more severe self-reported dysphagia ($\beta = 0.03$, 95% CI 0.01 to 0.04 , $p = 0.001$).

5.3 ASPECTS OF EMOTIONAL FUNCTIONING

5.3.1 Tension, worry, irritation and depressed mood at six months and five years after surgery

5.3.1.1 Study III

In **Study III**, 616 patients underwent surgery for oesophageal or cardia cancer during the study period. Of these, 506 patients (82%) were eligible for inclusion at six months following surgery, of whom 401 (79%) responded to the HRQOL assessment and were included in the analysis. Further, 153 patients were eligible at five years, and 140 (92%) of these were included in the five year analysis.

Based on the four questions constituting the emotional functioning scale incorporated in the EORTC QLQ C-30, 195 patients (49%) reported problems with tension, 246 (61%) with worry, 248 (62%) with irritation and 251 (63%) with depressed mood, at six months following surgery. At five years, 55 (39%) patients reported problems with tension, 69 (49%) worry, 63 (45%) irritation and 73 (52%) depressed mood. Moreover, of patients responding to both six month and five year assessments ($n = 116$), the majority of patients reporting emotional problems at six months also reported problems at five years (65%, 62%, 63% and 69% for tension, worry, irritation and depressed mood, respectively). However, a minority of patients who did not report problems at six months did report problems on all aspects of the emotional functioning scale (tension 15%; worry 18%; irritation 16%; depressed mood 24%, respectively) at five years post-surgery.

5.3.2 Potential risk factors for problems with emotional functioning

5.3.2.1 Study III

In **Study III**, patients diagnosed with squamous cell carcinoma as compared to adenocarcinoma had a higher likelihood of reporting problems with tension (OR 2.15, 95% CI 1.30–3.55), worry (OR 2.02, 95% CI 1.19–3.40), and depressed mood (OR 1.71, 95% CI 1.01–2.90) at six months after the operation. Fewer years of education as reflected by both nine-year compulsory schooling and upper secondary were observed as a risk factor for tension (OR 2.46, 95% CI 1.28–4.74 and OR 1.97, 95% CI 1.02–3.79, respectively), compared to higher education. Further, living alone was associated with a lower likelihood of problems with worry at both six months (OR 0.53, 95% CI 0.34–0.84) and five years (OR 0.35, 95% CI 0.15–0.84) following surgery, as compared with cohabitating patients.

5.3.3 Comparison with a Swedish reference population

5.3.3.1 Study III

Compared with a random sample from the Swedish background population, patients reported significantly more problems with emotional functioning at all assessments and for all aspects of emotional functioning (Figure 4). At six months post-surgery, the IRR for tension was 1.86 (CI 1.65–2.09), thus patients had a rate 1.86 times greater for reporting problems with tension compared with the background population. The IRR for worry was 1.71 (CI 1.57–1.87), the IRR for irritation was 1.68 (CI 1.54–1.83) and the IRR for depressed mood was 2.10 (CI 1.92–2.3). At five years post-operatively, the IRR for tension, worry, irritation and depressed mood were 1.55 (CI 1.24–1.94), 1.41 (CI 1.18–1.68), 1.27 (CI 1.05–1.54) and 1.77 (CI 1.49–2.1), respectively.

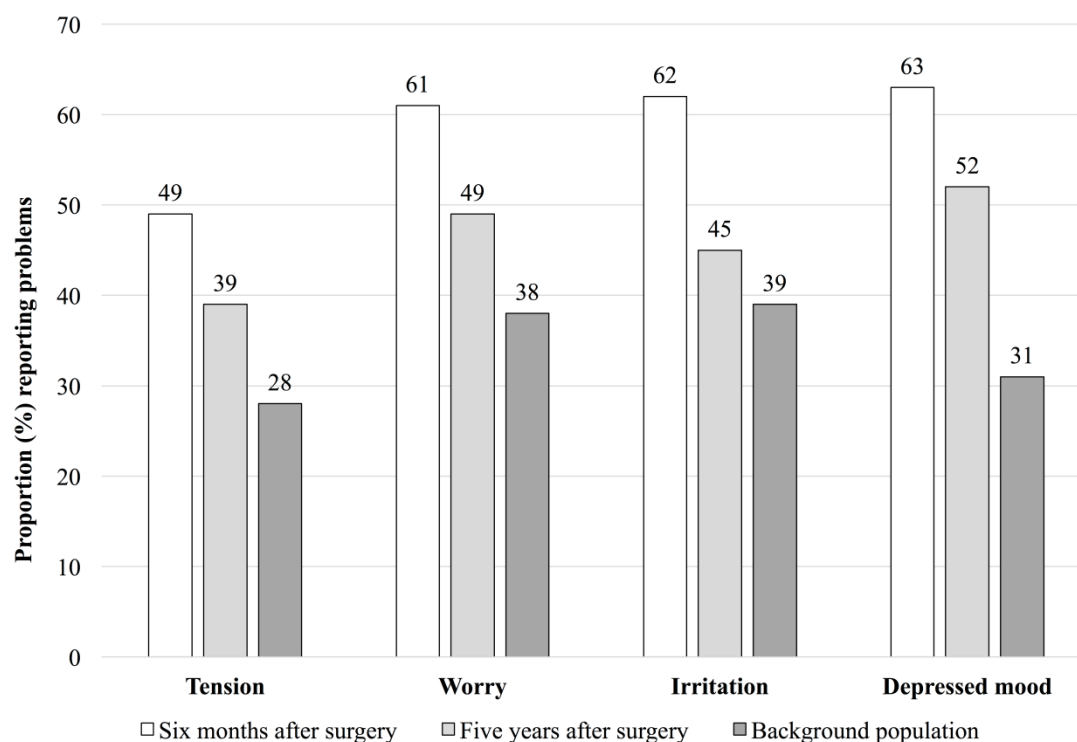


Figure 4. Proportion of patients reporting problems with the four items in the emotional functioning scale in the EORTC QLQ-C30 the SECC study at six months and five years post-surgery, as compared to a Swedish reference population.

5.4 PATIENT NARRATIVES ABOUT THEIR EXPERIENCES FROM DIAGNOSIS TO SIX MONTHS AFTER TREATMENT

5.4.1 Theme: “Undergoing a crisis reaction”

Six months following surgery for oesophageal cancer, patients’ narratives as described during open-ended face-to-face interviews, reflected the experiences of “Undergoing a crisis reaction”, forming as the overall latent theme in **Study IV** and illustrated in Figure 5.

Moreover, the theme comprised the three categories “From emotionally numb to feeling quite alright”, “From a focus on cure to reflections about a whole new life” and “From a severe treatment to suffering an emaciated, non-compliant body” derived from 14 distinct sub-categories identified from the patients’ narratives. The 14 sub-categories, three categories and the final theme are presented in Table 5. A significant transition in the patients descriptions of their adaptation, captured in the three categories, where a transition in feelings (i.e., “From emotionally numb to feeling quite alright”), reflections (i.e., “From a focus on cure to reflections about a whole new life”) and suffering (i.e., “From a severe treatment to suffering an emaciated, non-compliant body”) was observed.

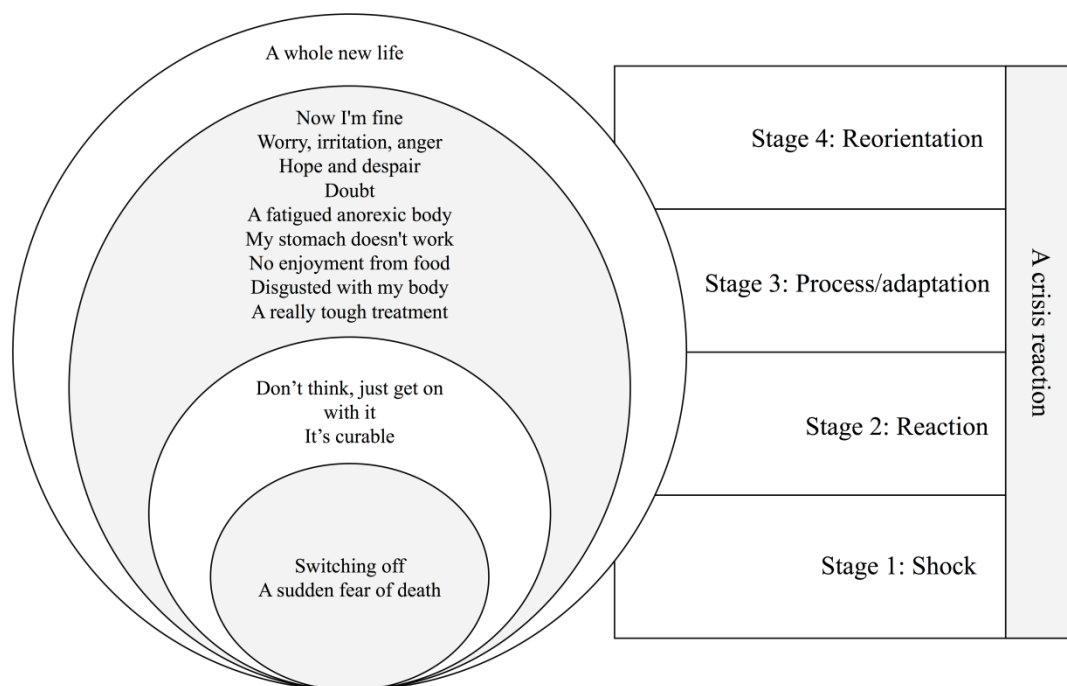


Figure 5. A schematic overview of the 14 sub-categories derived from the informants' narratives, six months following surgery for oesophageal cancer, in line with the four stages of a crisis reaction.

Table 5. An overview of the sub-categories, categories and theme as interpreted from the informants' narratives six months following surgery for oesophageal cancer.

SUB-CATEGORIES		CATEGORIES	THEME
<i>Then: At diagnosis and throughout treatment</i>	<i>Now: Six months following treatment</i>		
A sudden fear of death "Switching off"	Now I'm fine Worry, irritation and anger	From emotionally numb to feeling quite alright	Undergoing a crisis reaction
It's curable Don't think, just get on with it	Hope and despair Doubt A whole new life	From an increased focus on cure to reflections about a whole new life	
A really tough treatment	A fatigued anorexic body My stomach doesn't work No enjoyment from food Disgusted with my body	Suffering from a severe treatment and an emaciated, non-compliant body	

6 METHODOLOGICAL CONSIDERATIONS

6.1 QUANTITATIVE DATA

6.1.1 Accuracy

In order to evaluate the accuracy of the findings included in this thesis, the validity and the precision of the studies needs to be discussed. Both validity and precision relates to the amount of potential errors in all parts of the research process and impact on the accuracy of the study findings. Errors can either be random (happened by chance) or systematic (regularly introduced). Both random and systematic errors threaten the process of measuring the outcome in all observational studies, thus providing less accurate results [106].

6.1.1.1 *Random errors*

Random errors refer to the variability of the data and give information about the precision of a study. A high number of random errors means that a study lacks precision, however the number of random errors can decrease if the study size increases. One way this is reflected is in the width of the CI of the point estimate and the p-values. A CI is an expression of the statistical variability (i.e., random errors) behind the point estimate. The p-value is the arbitrary level of confidence. For example, in **Study III** the large sample size in the six-month analysis provided estimates with narrow confidence intervals, indicating that the observed estimate in the population sample and the true estimate lies within this narrow range, with 95% certainty (p-value < 0.005) [106]. However, the five-year assessment was hampered by limited precision, thus providing wider confidence intervals and less precise results. Moreover, **Study I** also included a relatively small sample, limiting the precision in the multivariable regression model for both anxiety and depression.

6.1.1.1.1 Type I and type II errors

Hypothesis testing was carried out in **Studies I – III**. No testing of a hypothesis is 100% certain, due to the testing of probabilities. Therefore, there is always a risk of committing a type I, or a type II error. A type I error is present when a statistically significant association is observed, even though there is no association in reality (i.e., a false positive result). Type II errors are the opposite, the statistical association is non-significant and the hypothesised association is ruled out, by mistake (i.e., false negative). The risk of committing a type I error can be decreased by lowering the statistical certainty with a lower p-value (i.e., alpha value). However all p-values in **Studies I – III** were set to the most established level of 95%. Further, the risk of committing a type II error is dependent on the statistical power of a study and can be reduced with an increasing sample size [106]. It is important to note that only 25%

of the patients diagnosed with oesophageal cancer are considered for curatively intended treatment, thus limiting the obtainable sample size possible in any one year.

6.1.1.2 Systematic errors

Systematic errors, also called bias, affect the study validity. Increasing the study sample in a given study cannot reduce systematic errors. Systematic errors are divided into selection bias, information bias and confounding [106].

6.1.1.2.1 Selection bias

Selection bias relates to the sampling procedure of a study. How have the participants been included and did something affect participation or not? Selection bias may produce a different association between exposure and outcome within the study population as compared to the non-participants [106]. There is a risk of selection bias in all observational studies included in this thesis (i.e., **Studies I – III**), due to non-participation and missing data. The non-participation is particularly observed in the follow-up assessments in **Studies II** and **III**, where for example, a few participants were too ill to participate. This introduces a risk of a “healthy workers effect”, where the study participants are healthier than the larger study population from which they were drawn [106]. However, in an attempt to evaluate the amount of selection bias in **Studies I – III**, statistical comparisons between responders and non-responders regarding patients’ characteristics were carried out. In **Study I** squamous cell carcinoma was statistically more common among non-responders than responders. Possibly this could be explained by differences in risk profile from patients with adenocarcinoma [19]. In addition, a less advanced tumour stage was also observed as more common among non-responders, than responders, for reasons not explained. In **Study II** in-hospital complications were more common at six months among responders of the PROM assessment, compared to non-responders at six months. However, this could possibly be explained by the fact that patients with in-hospital complications were treated at STH at the time of the follow-up assessment, meaning that the questionnaires were administered by the data collector at the hospital instead of being sent to the patients’ home. In **Study III**, there were no statistical differences in patient characteristics, between responders and non-responders, either at the six-month assessment or the five-year follow up, indicating a lower risk of selection bias.

6.1.1.2.2 Information bias

Information bias, also called misclassification bias, refers to misclassification of the study outcome or exposure. Misclassification of exposure variables (i.e., clinical and socio-demographic characteristics) in **Studies I – III** cannot be ruled out. However, possible

misclassification was reduced by the thorough review of medical records according to pre-defined study protocols in all studies. Also the extensive collaboration including e.g., pathologists, surgeons, contact nurses and research coordinators included in the clinical data collections in England (**Studies I – II**) and in Sweden (**Study III**), reduced the amount of misclassification of exposure variables. Further, misclassification of outcome variables i.e., anxiety and depression in **Studies I – II** and aspects of emotional functioning (i.e., tension, worry, irritation and depressed mood) in **Study III**, needs to be discussed in more detail. Anxiety and depression were measured using the HADS, which has been considered as a valid and suitable screening instrument for psychological distress in cancer patients in the in-hospital care setting [107]. However, the HADS is not recommended as a diagnostic instrument yielding a diagnosis of anxiety or depression by a clinical interview [89] based on criteria in the DSM V [71]. Consequently, the HADS, as a brief self-report screening instrument, may only capture a limited part of significant aspects of anxiety and depression that patients in **Studies I – II** experienced. Moreover, the reliability of the HADS, assessed in terms of sensitivity and specificity of caseness of anxiety and depression have been found to vary [89]. A test that is 100% sensitive finds all true cases and a test that is 100% specific rules out all non-cases. This is important when evaluating misclassification of outcome for a screening instrument. The sensitivity and specificity for both the anxiety and the depression subscales have been set to an overall value of 0.8 [108]. The highest values for sensitivity and specificity have been shown for a cut-off of scores ≥ 8 for each of the subscales [89]. The established cut-off was used in **Studies I – II** in the present thesis. Further, in an attempt to reduce the risk of possible misclassification of the outcome measure in **Study III**, each of the four aspects comprising the emotional functioning scale in the EORTC QLQ-C30 were analysed separately in the multivariable models, due to the risk that summary scores on item responses may disguise different item responses. Further, the somewhat rough categorisation of the responses to each of the four items into ‘problems’ versus ‘no problems’ might contribute to the high proportion of patients reporting problems on each of the four items. This might limit the information of the symptom burden of tension, worry, irritation and depressed mood.

6.1.1.2.3 Confounding

Confounding means that a third factor distorts the association between the exposure and the outcome. A confounding factor is associated with both the exposure and outcome, independently and is not a mediator of any effects identified between the exposure and the outcome under study. In order to reduce confounding in **Studies I – III**, multivariable logistic

regression and mixed-effects models were used in order to adjust the analysis for known factors that might influence the associations observed. However, a major limitation with all quantitative studies included in this thesis is the lack of information on psychiatric variables e.g., history of psychiatric disorders, prescription of psychotropic drugs and use of psychiatric in-hospital care or out-patient care, which repeatedly has been shown to be associated with psychological distress [86, 109]. Therefore, all findings should be interpreted with caution in the light of these known and unknown potential confounding factors.

6.1.1.2.4 Measurement validity

A valid instrument measures what it intended to measure. One way of evaluating this when conducting research with survey data is by investigating the psychometric properties of the questionnaire. In brief, Cronbach's alphas were 0.89 for the anxiety subscale and 0.83 for the depression subscale of the HADS, indicating satisfactory internal consistency [26].

Moreover, the PCA revealed a two-factor structure explaining 56.86% of the variance. The rotated factor structure found the anxiety items of the HADS loading satisfactorily onto the first factor, and the depression items loading satisfactorily on the second factor. However, item 7 'I can sit at ease and feel relaxed', loaded highly on both factors, as has been observed previously [104]. This means that it is difficult to distinguish whether item 7 measures symptoms of anxiety or symptoms of depression.

6.1.1.2.5 External validity

The external validity of a study refers to the generalisability. The psychological distress experienced by patients diagnosed with oesophageal cancer, might be generalised to other cancer groups, diagnosed with a highly fatal cancer. However, the particular impact on eating and eating difficulties associated with the treatment might be difficult to compare. Thus, patients diagnosed with head and neck cancer or gastric cancer are very similar in many aspects of the recovery process.

6.2 QUALITATIVE DATA

When discussing the methodological strengths and weaknesses of qualitative studies, different concepts, are used from those in quantitative study terms. In qualitative research a study's trustworthiness is evaluated by addressing the credibility, dependability and transferability [110]. In addition a naturalistic inquiry is used, meaning that the focus is not on the generalisability of the results, rather on the context within which the study was carried out, and the research findings should be interpreted and understood in the light of this context.

6.2.1 Credibility

Credibility refers to the researcher's whole approach to the study and covers the aim of the study, the context where the study was carried out, the selection of participants and the various experiences the informants contribute with. It also includes how well the categories and themes cover the gathered data [111]. According to Guba [112], the credibility of a study can increase through, for example, peer debriefing and triangulation during the study procedure. A study with good credibility produces plausible findings; consequently, low credibility leads to findings that are difficult to interpret. In **Study IV** the rationale of the study was clear; in order to address the overall aim of this thesis, by highlighting the psychological distress experienced and the need for psychological support in this patient group, using different research methods. A deeper understanding of the patients' experiences, needs and perspectives was made possible. Further, the data collection of **Study IV** was explained in detail, incorporating an explanation of the study context, study participants and the analysis process. In addition, the research findings were thoroughly explained, in an attempt to enhance the reader's ability to assess the credibility of the study and interpret the findings in light of the actual context.

6.2.2 Dependability

Dependability discusses to the extent of how much data change over time. It also covers modifications of the researchers' decisions during the analysis process [102]. Guba [112] suggests that overlapping methods and stepwise replications of the analysis process can be used in order to produce findings that are stable. Low dependability results in instability of the study findings. In **Study IV** the data did change over time, as the analysis process progressed. However, even though the codes, sub-categories, categories and themes were re-formed several times, following discussion between the authors of the study, the core of the patients' narratives was stable across time.

6.2.3 Transferability

In order to reach transferability, a comprehensive collection of descriptive data is recommended as well as purposive sampling and an adequate presentation of research findings. High transferability produces findings that are relevant according to the described context and low transferability refers to findings that are not comparable to other study settings [112]. In **Study IV**, a comprehensive data collection was accomplished by in-depth interviews with open-ended questions and follow up questions in order to enrich the material. However, the transferability of research findings to other cancer groups is restricted to groups that suffer from major eating difficulties as a result of an extensive operation in an area that

affects the physical eating functioning. Considering the changed eating ability in combination with a poor prognosis and the challenging recovery process one cancer diagnosis that might be comparable with oesophageal cancer is head and neck cancer.

7 DISCUSSION

7.1 GENERAL DISCUSSION OF FINDINGS FROM STUDIES I – IV

Study I showed that 34% of patients reported anxiety and 23% reported depression, according to the pre-defined cut-off (i.e., scores ≥ 8 on each subscale) of possible-probable caseness of anxiety and depression measured by the HADS, prior to oesophageal cancer surgery. In addition, 14% of the patients reported co-morbid anxiety and depression, suggesting that a proportion of patients are particularly burdened by psychological distress prior to treatment. The severity of overlapping symptoms of anxiety and depression has been reported previously and a prevalence rate of 12.4% has been observed in a mixed cancer group [113]. However, it is suggested that overlapping symptoms might be associated with, for instance, poorer treatment outcomes [114].

In previous studies screening for anxiety and depression in mixed cancer diagnoses where patients were screened the day before cancer surgery, prevalence rates of 19% for anxiety and 14% for depression have been reported [115]. However, the prevalence rates reported were based on a cut off corresponding to scores ≥ 11 on each of the subscales; higher than the recommended cut-off used in **Study I**. Further, in other areas of major abdominal surgery, e.g., bariatric surgery prevalence rates of 16.8% of current anxiety disorder and 32.7% of current depressive disorder, have been diagnosed in face-to face interviews (i.e., the diagnostic interview SCID) prior to surgery [116]. Within bariatric surgery pre-operative assessments of psychological distress have become a requirement for patients considered for surgical the intervention [117], due to the successful contribution of intervention to the final outcome [118], as compared to previously undiagnosed psychological conditions [117]. Taking this into account, pre-treatment psychological assessments may also be suggested for oesophageal cancer patients, based on for instance, the similar pre-surgical prevalence rates observed between the groups.

Study II indicated that anxiety symptoms remained stable from pre-surgery up to six and 12 months post-surgery. Nevertheless, depression symptoms increased from pre-surgery to six months after the operation, levelling off between six and 12 months post-operatively. The course of psychological distress presented in **Study II**, is in line with previous results investigating longitudinal anxiety and depression during the first year post-diagnosis. The study showed levels of anxiety highest at diagnosis and levels of depression highest during treatment (at six months post-diagnosis). However, the sample included both operable and

palliative oesophageal cancer patients [13]. Further, in a prospective cohort study investigating the course of anxiety and depression during the first year post-operatively, 55% of the patients moved from reporting no anxiety to anxiety over time, and 76% of the patients reported deterioration in depression scores [12]. The study included oesophageal cancer survivors assessed by self-reports of the HADS, using the same cut-off as in **Study II**.

In **Study III**, the long-term prevalence of psychological distress was assessed, at six months and five years post-surgery. When using the items tension, worry, irritation and depressed mood, incorporated in the emotional functioning scale (EORTC QLQ C-30) and used as a proxy for anxiety and depression, a substantial proportion of patients reported problems at six months (tension 49%, worry 61%, irritation 62% and depressed mood 63%), persisting in the vast majority of the patients at five years (tension 39%, worry 49%, irritation 45% and depressed mood 52%). This result is contradictory to a few earlier studies that have suggested that emotional functioning assessed by the EORTC QLQ-C30 seems to improve over time, as compared to baseline values [119, 120]. However, a recent prospective cohort study carried out in long-term survivors of oesophageal cancer 10 years following the operation, revealed that patients do not recover in any of the aspects of HRQOL (including emotional functioning) between five and 10 years. In addition, compared to a Swedish reference population the survivors reported worse HRQOL at 10 years post-surgery [59]. The comparison with the reference population is consistent with the findings of **Study III**, where patients reported significantly more problems with tension, worry, irritation and depressed mood at six months and five years post-operatively. Further, the majority of patients reporting problems at six months also reported problems at five years in **Study III**. However, a small sub-group of patients had deteriorated by five years. This deterioration has been observed earlier in a sub-group of patients regarding HRQOL assessments five years after treatment [58].

Self-reported dysphagia (i.e., swallowing difficulties) and limitations in activity status were the two main risk factors that emerged as predictors of elevated anxiety and depression during the course of the first post-operative year (**Study II**). Self-reported dysphagia has not only been reported as one of the main symptoms pre-surgery [24], it has also been shown that more than 30% of oesophageal cancer patients report deterioration in dysphagia over time, even up to five years post-surgery, reducing HRQOL [58]. Similarly, dysphagia has also been addressed as one of the main persisting symptoms in head and neck cancer survivors [121], highlighting the similarities in clinical presentation of post-operative symptoms between

oesophageal cancer and head and neck cancer. Further, post-operative dysphagia is not only a major risk-factor for malnutrition and poor HRQOL [57, 122], it has also been shown to be associated with a loss of pleasure when eating, affecting the patients' social life and well-being [123]. In an attempt to address the possibility that dysphagia also could be explained by recurrent disease, an independent t-test was carried out in **Study II**, showing that anxiety and depression and dysphagia did not differ among patients with and without recurrent disease, during the first year. Importantly, whether the self-reported dysphagia assessed in **Study II** was structural, functional or even psychosomatic by nature remains unexplained.

Moreover, poor physical status is a known risk factor for depression [124, 125] also observed in **Studies I and II**. In addition, in-hospital complications predicted elevated depression scores in **Study II** and might be explained as patients with in-hospital complications suffering poorer physical condition. Consistent with previous studies, younger age and female sex were associated with increased anxiety levels [125, 126], also observed in **Studies I – II**. Living alone was observed as a risk factor for anxiety in **Study II**. The positive impact of spousal support is well established in the cancer literature (e.g., [127, 128]). Contradictory, non-cohabitating patients were less likely to be worried in **Study III**, for reasons not known. Further, squamous cell carcinoma and lower educational attainment were associated with tension in **Study III**. Previous research suggests that squamous cell carcinoma have a different risk profile including lower education level and socio-economic status as compared to adenocarcinoma [129]. This has also been observed in head and neck cancer where lower socio-economic status and unemployment were predictors of poor quality of life up to five years after the end of treatment [130]. The possible correlation with psychological distress has also been suggested [131].

The patient narratives in **Study IV**, describing the experiences during the first six months after curatively intended treatment for oesophageal cancer, were interpreted as reflecting a crisis reaction. The narratives demonstrated a clear transition in the patients' mental status during this early period of recovery. According to the Swedish rehabilitation program for cancer survivors [132] it is common that cancer patients undergo a crisis reaction as per of a natural response to the diagnosis and treatment. The programme suggests that all information given should be adapted to the patients' current situation and all health-care professionals managing cancer patients should be able to adequately respond to a person in crisis.

7.2 INTERPRETATIONS

The findings from this thesis indicate that patients undergoing curatively intended treatment for oesophageal cancer report significant psychological distress from pre-surgery up to five years post-surgery in the form of anxiety, depression as well as tension, worry, irritation and depressed mood. In addition, patient narratives also reflected that oesophageal cancer patients undergo the different stages of a crisis reaction. However, whether this potential crisis reaction will progress adaptively or whether patients will develop persisting symptoms is too early to evaluate at six months following surgery. Nevertheless, findings included in this thesis have shown that a considerable number of patients report psychological distress at six months, 12 months and even up to five years post-treatment. Whether psychological distress is due to a prior history of psychological morbidity, severe and long-lasting physical symptoms associated with the disease in particular (i.e., dysphagia or physical limitations), or a disturbance in the progression of the crisis reaction causing a “locking effect” and symptom development e.g., anxiety and depression or irritation, over time, remains unsolved. However, Cullberg [70] schematically described the consequences of an unprocessed crisis reaction (Figure 6). Interpreting this process in the context of oesophageal cancer shows that how well a patient copes with the reaction process (mobilisation of defence strategies) will have consequences for the further development of successful rehabilitation (i.e., reorientation) or impaired adaptation (i.e., poor emotional recovery).

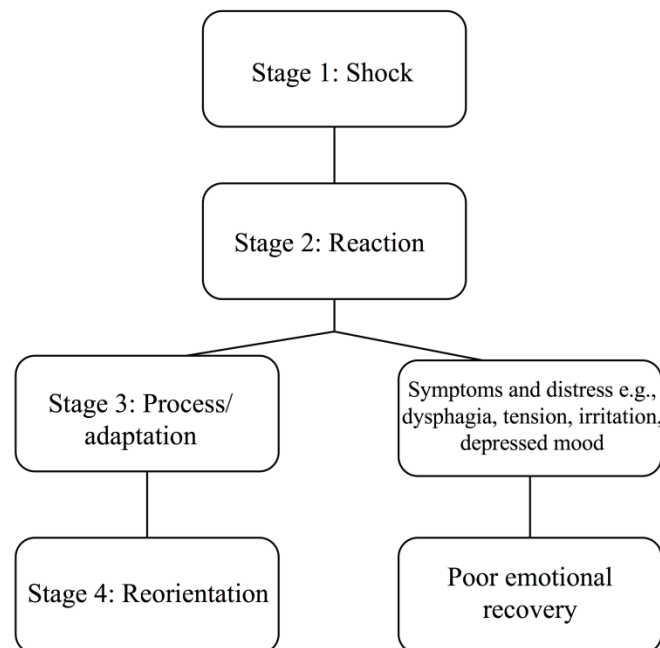


Figure 6. A schematic overview of a crisis reaction process.

In line with a more psychodynamic orientated interpretation [133], the long-term psychological distress experienced by oesophageal cancer patients may be understood as follows. When a trauma is unexpected and the individual is unprepared, the shock reaction at the time of the trauma can be missed out and delayed, thus occurring several years after the traumatic event. However, after a few years when the individual begins to adapt to their new life situation, the shock reaction may return and cause traumatic emotions to emerge that were repressed at the time of the trauma. The psychological support needed in case of a delayed shock effect should focus on processing the traumatic event in a non-threatening environment (i.e., in therapy) where the traumatic experiences can be put into words and the emotions related to the trauma experienced.

7.3 CLINICAL IMPLICATIONS – IS THERE A NEED FOR PSYCHOLOGICAL SUPPORT?

The clinical implications of this thesis are as follows. To date, only a minority of cancer centres around the world (e.g., United States, UK, Canada), have implemented screening of psychological distress in patients using standardised tools [77]. This is despite the evidence that successful detection of psychological conditions prior to surgery in e.g., bariatric surgery, contributes successfully to the final outcome [117].

- Considering the distress observed in this thesis, results suggest that all patients diagnosed with oesophageal cancer should be routinely assessed in order to identify those with current psychological distress and those at risk of developing psychological distress over time.

In order to improve the psychological recovery for patients that are particularly affected by symptoms related to post-operative eating difficulties (i.e., dysphagia), interventions investigating the psychological and/or social aspects of eating have been addressed [134]. In addition, swallowing functional training in dysphagic tongue cancer patients has been shown to reduce the severity of post-operative depression [135].

- Considering the observed association of dysphagia and psychological distress, the thesis findings suggest that patients burdened by dysphagia following surgery should be investigated in order to identify whether the swallowing problem is caused by recurrent disease, functional problems related to the resection, or are psychosomatic by nature.
- Should post-operative dysphagia be psychosomatic, specific therapeutic interventions aiming to helping patients cope with the symptom and adapting to their new life

situations are required, as a development of the need addressed by e.g., Cousins et al [134].

As shown in Figure 6, disruption in the reaction phase may result in the development of symptoms of psychological distress and poor recovery. This might be explained by differences in defence strategies affecting the patient's emotional reactions during the illness trajectory. An adaptive response to a crisis reaction would include a progression through the four stages, and mobilising adaptive coping strategies during the reaction phase (stage 2). However, a maladaptive response would include the mobilisation of defence strategies (instead of coping) and repression of the basic emotions experienced during the reaction phase, leading to a "locked" progression.

- One interpretation of the psychological distress observed in this thesis, based on affect focused therapy [66] is that patients may be experiencing a "locked" reaction phase thus leading to symptom development (e.g., anxiety and depression). Based on this theoretical framework, patients reporting such distress should be offered psychotherapeutic interventions, if wanted, focused on experiencing the repressed adaptive emotion (i.e., anger, grief), and reducing inhibitory emotions and maladaptive defence strategies.



"In therapy"

8 CONCLUSIONS

- A substantial number of patients report psychological distress prior to surgery and then at six months and five years after curatively intended treatment for oesophageal cancer.
- Longitudinal findings suggest that anxiety seems to remain stable during the first 12 months, while depression increases between pre-surgery and six months, levelling off between six and 12 months post-surgery.
- Important risk factors for psychological distress might be self-reported dysphagia, physical limitations, living alone and female sex.
- Patient narratives describing the first six post-operative months, reflects the experiences of undergoing a crisis reaction.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

9.1 BAKGRUND

Cancer i matstrupen (esofagus) eller i övre magmunnen (cardia), drabbar årligen cirka 600 personer i Sverige och cirka 480, 000 personer i Storbritannien. Denna avhandling baseras på data från både Sverige och England. I Sverige är matstrupscancer en relativt ovanlig cancerform som dock har en synnerligen dålig överlevnadsprognos då den ofta upptäcks i ett sent skede. Anledningen till den sena upptäckten är matstrupens elastiska förmåga. Det bidrar till att en tumör kan växa under lång tid i matstrupen eller i magmunnen och ge få symtom. Det vanligaste symtomet är sväljsvårigheter, det vill säga att maten fastnar i halsen, kommer upp igen eller en känsla av att det är svårt att få ner maten. På grund av att matstrupscancer ofta upptäcks i ett sent skede är endast cirka en fjärdedel av de som diagnostiseras i fysiskt skick att genomgå behandling med syfte att bota patienten. Majoriteten av de som drabbas kommer alltså inte att genomgå botande behandling. Denna avhandling fokuserar på den grupp av patienter som genomgår behandling för matstrupscancer där syftet är att bota.

Behandlingen av matstrups- och övre magmuncancer innebär omfattande kirurgi. Operationen syftar till att ta bort tumören och det närliggande området. Detta kombineras med cellgiftsbehandling. Här skiljer sig Sverige och Storbritannien åt. I Sverige är det vanliga vårdförloppet att cellgiftsbehandling ges enbart innan operation och i England att cellgiftsbehandling ges såväl innan som efter operationen. Cellgiftsbehandling ges av framförallt tre skäl; för att minska tumören så den blir lättare att operera bort, för att minska eventuella sväljsvårigheter och framförallt, för att minska risken för mikroskopisk spridning av cancerceller (det vill säga spridning av enstaka canceromvandlade celler). Kirurgi som syftar till att ta bort en tumör i matstrupen eller övre magmunnen är ett mycket omfattande ingrepp, ett av de största planerade kirurgiska ingreppen som görs i Sverige och i England. Operationen innebär vanligtvis att hela, eller delar av matstrupen/magmunnen tas bort och att det bortopererade området ersätts med en bit av magsäcken. Det betyder att magsäcken blir mindre och dras upp i halsen, där den sys ihop med en resterande frisk del av matstrupen. I samband med operationen finns dessutom risk att skada nerver och närliggande vitala organ så som luftstrupen, hjärtat eller lungorna. Även för de som genomgår kirurgi med syfte att bota är prognosen dyster. Endast cirka 40 % av patienterna lever fem år efter behandling.

Att genomgå behandling för cancer i matsstrupe/magmun innebär stora medicinska risker, omfattande fysisk påfrestning och påverkan på en persons livskvalitet på både kort och lång

sikt. Operationen för med sig stora svårigheter att äta på grund av att matstrupen opererats bort och ersatts. Några av de symptom som patienterna lider av i efterförloppet är kraftig viktnedgång, sväljsvårigheter, matleda, smärta, sura uppstötningar och diarré. Detta har en negativ påverkan på patienternas återhämtning. Dessutom finns det en hög risk att cancer kommer tillbaka. Denna risk är högst under det första året efter operationen. Detta skapar naturligtvis en oro hos patienterna och vid återfall finns det i dagsläget inget nytt alternativ att operera patienten igen och avlägsna cancertumören. Den behandling som kan ges syftar istället till att lindra eventuella symptom.

Under de senaste tio åren har forskningen om matstrupscancer gått framåt. Inom områden som behandlingsstrategier, överlevnad och livskvalitet har detta lett till stora förbättringar för patientgruppen. Den psykologiska påverkan på individen av en sådan omfattande behandling som matstrupscancerbehandling innebär, har dock inte klarlagts och förbättrats på samma sätt som övriga forskningsområden.

De främsta anledningarna till att vi valt att studera den psykologiska påverkan efter behandling för cancer i matstrupe/magmun är för det första matstrupens viktiga funktion, för det andra den symboliska innebörden av att kunna äta, för det tredje den tuffa behandlingen, för det fjärde den svåra rehabiliteringsprocessen och slutligen, för det femte den dåliga långtidsprognosen.

Det övergripande syftet med denna avhandling var att undersöka psykologiska konsekvenser av matstrupscancerbehandling och detta gjordes med hjälp av fem specifika forskningsfrågor:

- 1) Vad är prevalensen (förekomsten) av och riskfaktorer för ångest och depression före matstrupscancerkirurgi?
- 2) Vad är prevalensen av ångest och depression över tid (upp till ett år efter behandling)?
- 3) Vad predikterar ångest och depression över tid?
- 4) Hur ser den längre psykologiska återhämtningen ut, upp till fem år efter kirurgi och vilka faktorer predikterar dålig återhämtning över tid?
- 5) Vad säger patienterna själva om de sex första månaderna efter behandling?

9.2 METODER

Studie I var en tvärsnittsstudie där 106 patienter besvarade ett frågeformulär som mätte ångest och depression dagen innan canceroperation. Studien genomfördes i England på St Thomas' Hospital i London under perioden 1:a november 2011 till och med 1:a mars 2016.

Studie II var en långtidsuppföljning (kohortstudie) av patienter som opererats för matstrupscancer under samma tidsperiod som **Studie I**, på samma sjukhus. Patienterna fick fylla i frågeformulär som mätte ångest och depression vid tre tillfällen. Innan operation, och sex respektive 12 månader efter operation. Tvåhundraarton (218) patienter deltog i mätningen som ägde rum innan operationen, 139 patienter fyllde i frågeformulär sex månader efter operationen och 129 patienter fyllde i frågeformulär 12 månader efter operationen. Enkäterna för den första mätningen administrerades på sjukhuset dagen innan operation. Vid de uppföljande tillfällena efter operation skickades enkäterna hem till patienterna. **Studie III** var även denna en långtidsuppföljning (kohortstudie) innehållande patienter som opererats för cancer i matstrupe eller magmun i Sverige, mellan 2:a april 2001 och 31:a december 2005. Denna studie mätte psykologiska aspekter av sjukdomen och behandlingen genom fyra frågor som rörde om patienterna upplevt sig spända, oroliga, irriterade eller nedstämda, under den sista veckan som gått. Vid sex månader efter cancerkirurgi följdes 401 patienter upp med frågeformuläret innehållandes dessa frågor. Vid fem år efter operation deltog 140 patienter i enkätuppföljningen. Enkäterna skickades vid samtliga tillfällen hem till patienterna. **Studie IV** var en kvalitativ studie där 10 patienter som opererats för cancer i matstrupen intervjuades om hur de mått under de sex första månaderna efter operationen. **Studie I – III** analyserades med kvantitativa metoder som till exempel regressionsanalys (**Studie I, III**) och faktoriell variansanalys (ANOVA) (tvåvägs [**Studie II**]). Den kvalitativa intervjustudien analyserades med hjälp av innehållsanalys.

9.3 RESULTAT

Resultat från **Studie I** visade att 34 % av de patienter som ska opereras för cancer i matstrupe/magmun har ångest, dagen före kirurgi och 23 % rapporterar att de känner sig nedstämda (deprimerade). Fler kvinnor i studien rapporterade ångest jämfört med män och de patienter som upplevde sig fysiskt begränsade av sin sjukdom var i högre grad deprimerade, jämfört med de som inte rapporterade några fysiska begränsningar. Resultat från **Studie II**, visade att ångestnivån ser ut att ligga på samma nivå i patientgruppen över tid. Det vill säga lika mycket ångest som rapporterades dagen innan operation, rapporterades även vid sex- och 12-månadersuppföljningen. Depressionsnivån däremot, var som lägst dagen innan operation, för att sedan öka mellan första mättillfället och sexmånadersuppföljningen och därefter plana ut något mellan sex- och 12-månadersmätningen. Riskfaktorer för ångest och depression över tid i **Studie II**, visade sig framförallt vara självrapporterade sväljsvårigheter, fysiska begränsningar, kvinnligt kön och att vara ensamboende. **Studie III** visade att 49 % av patienterna kände sig spända, 61 % var oroliga, 62 % var irriterade och 63 % upplevde

nedstämdhet sex månader efter operationen. Fem år efter operationen kände fortfarande 39 % av patienterna sig spända, 49 % var oroliga, 45 % var irriterade och 52 % kände sig nedstämda. Låg utbildningsnivå var en riskfaktor för att känna sig mer spänd vid sex månader efter operationen. Intressant nog visade det sig att patienter som var ensamboende vid tiden för operationen, var mindre oroliga både vid sex- och femårsuppföljningen. I **Studie IV** reflekterade patienternas egna berättelser en pågående krisreaktion och en transition, det vill säga en märkbar skillnad i deras sätta att uttrycka sig om dåtid (vid diagnostillfället) och nutid (sex månader efter behandlingen).

9.4 SLUTSATS

En stor andel av de patienter som opereras för cancer i matstrupen mår psykiskt dåligt före, under och efter behandlingen. Nivån av ångest verkar vara mer eller mindre beständig över tid upp till 12 månader efter operation. Nivån av nedstämdhet (depression) ökar initialt, men med en förhållandevis låg takt. Vid sex månader stiger nivån av nedstämdhet (depression) markant för att därefter stanna på en relativt hög nivå. Vid fem år efter operationen svarar majoriteten av patienterna att de fortfarande känner sig, spända, oroliga, irriterade och nedstämda. De främsta riskfaktorerna för försämrad psykologisk återhämtning är självrapporterade sväljsvårigheter, fysiska begränsningar och kvinnligt kön.

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